THE AMERICAN JOURNAL OF ROENTGENOLOGY
RADIUM THERAPY AND NUCLEAR MEDICINE

VOL. 86 OCTOBER, 1961 No. 4

RADIATION THERAPY OF CANCER*

CURRENT RESULTS WITH MEGAVOLTAGE AND ORTHOVOLTAGE

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RADIATION therapy, skilfully employed, continues to be a prime weapon for the cure and palliation of certain types of cancer. For localized cancer of sites such as skin, lip, oral cavity, eyelid and larynx, it provides cure rates equal to or better than those obtainable by radical surgery, and with *superior functional* results;[12] for cancer of the cervix it provides in general *better cure rates* than does surgery, with lower morbidity and mortality;[10] for lymphoblastoma and chronic leukemia it provides somewhat safer treatment than chemotherapy, with *less morbidity*.[12] For certain tumors no longer localized, such as seminoma testis and medulloblastoma cerebelli, it provides a goodly percentage of five year arrests. For selected cases of breast and endometrial cancer, it also provides long term control.

One of the questions facing the physician attending a patient with cancer (and certain other diseases suitable for radiation therapy) is: "Should I recommend supervoltage—or telecobalt—therapy?" That is, "Will megavoltage be better for my patient?" While this decision is normally best left to the treating radiologist, there are circumstances under which the patient expects the attending or family doctor to speak out. The purpose of this paper is to set forth certain facts in order to help him answer the question.

DEFINITIONS

Supervoltage therapy devices include roentgen-ray units operating in the 800 kv. to 2,000 kv. range, and for all practical purposes radioactive cobalt and cesium teletherapy units. The former have been in use for some thirty-two years, and cobalt 60 teletherapy units for about twelve years. Many radiologists use the term *megavoltage* for these devices, in order to avoid the tenuous connotation of the prefix "super." The *biologic* (cancericidal) effect of supervoltage radiation as ordinarily measured, is actually "infra" or inferior to that ob-

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Presented in part at the Cancer Conference of the American Society of Oral Surgeons, Phoenix, October 10–12, 1960.
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tainable with rays in the 250 kv. range.[10]

The so-called *effective* voltage of many roentgen-ray beams is considerably lower than the *peak* voltage, and is a better clue to their relative penetrating power. The latter is also recorded in terms of the thickness of a standard material, such as copper, which will reduce the transmitted radiation beam by a factor of one half (the HVL or half value layer equivalent factor). This may be recorded in other materials such as water, aluminum or lead, but for convenience of ready comparison the half value layer in copper of several different radiation beams is listed in Table 1.

The term *orthovoltage* deep therapy is applied to 200–400 kvp. roentgen-ray beams, the equivalent effective voltage of which is from 0.07 to 0.12 million electron volts or mev.*

The term *megavoltage* deep therapy, or supervoltage, is applied to conventional roentgen-ray beams in the 1,000 kvp.–15,000 kvp. range, that is, one to fifteen million volts; the real or effective voltages of these beams range from 0.5 to 5 mev. The beams may be from linear accelerators and other sources. Iridium 192, cesium 137, cobalt 60 and radium teletherapy units yield hard roentgen rays or gamma rays in or close to this effective voltage range (see Table 1).

The term *ultra-high voltage* deep therapy is employed for betatrons (in the 10–50 mvp. range), synchrotrons and similar high energy devices used to produce hard roentgen rays as well as electron beams and so forth. Neutron, proton and certain other beams may be included in this category.

The radiologist also has available low voltage roentgen-ray beams (50 kvp.–150 kvp.), as well as beta and alpha "ray" beams derived from natural or artificial radioactive materials.

There are many devices for applying, aiming or modifying *external* radiation beams, including equipment for: *fixed beams; moving beams* (rotation, arc, spiral, pendulum and traveling beams); and *re-*

* The Joint Commission of the International Atomic Energy Agency and the World Health Organization meeting in Vienna, August, 1959 defined orthovoltage as being in the 200–400 kv. range.

TABLE I

SOME EXTERNAL RADIATION SOURCES

Term	Source (usually peak voltage)	Approximate mev. Equivalent	HVL mm. Cu*	Relative Biologic Equivalent
Orthovoltage deep therapy	250 kv. roentgen ray	.1	1–3	1
Megavoltage deep therapy	1,000 kv. roentgen ray	.5	8	.75–.85
	Cs^{137} teletherapy	.6	8	
	Radium teletherapy	.8	13	
	Co^{60} teletherapy	1.2	14	
	"6 million" volt linear accelerator	1.6	15	
Ultra-high voltage therapy	23 mv. roentgen ray	8	"32"	?.75
	70 mv. roentgen ray	23	"33"	

* Copper is used in this table to permit ready comparisons; in ordinary practice lead is used above 1,000 kv.

stricted beams (grid-therapy and wedge filter therapy).

With these devices radiations may be circumscribed, "pinpointed," "aimed," "localized" and otherwise applied with varying degrees of precision. Roentgen or gamma rays cannot, of course, be focused.

Radiations may be applied internally via: intracavitary cones or cylinders; interstitial tubes, needles, seeds, threads, colloidal suspensions and solutions; intravascular injections; and intracavitary instillations.

Basic principles of effective radiation therapy of cancer may be defined as follows:

1. Determination of the *histologic type* and estimation of the *anatomic extent (or stage) of the tumor.*

2. Determination of the *clinical status of the patient;* some patients with cancer may be too ill from other disorders to warrant radical therapy of the neoplasm.

3. Selection of the *treatment modality* apt to result in the least physical and economic trauma; this modality may be orthovoltage, megavoltage, cobalt 60, radium or other means.

4. *Meticulous planning and application* of irradiation, with deliverance of an optimum dose to the tissue of interest.

5. Provision for necessary associated medical and surgical treatment.

6. Conscientious *after care and follow-up.*

Radiosensitivity constitutes responsiveness to radiation in terms of tumor cell destruction, but with regeneration and recuperation of adjacent normal cells. It is a complex phenomenon, depending on many factors such as tumor cell type, tumor size, blood supply, infection, anatomic location and other factors. *It cannot be predicted from the microscopic appearance* and is not synonymous with radiocurability. Many localized squamous cell tumors are relatively insensitive (requiring large doses of radiation for cure), but *are* quite radiocurable. Conversely, some lymphomatous tumors are very radiosensitive, but are seldom curable. *Radiocurability* depends on factors such as the tumor cell type, the size of the tumor, its anatomic extent, the tolerance of adjacent structures, the degree of natural drainage and so forth. A localized adenocarcinoma of the cervix uteri is usually radiocurable; a lymphosarcoma of the tonsil, with mediastinal lymph node spread usually is not.

A curative dose for localized carcinoma is defined as that dose which is destructive of tumor cells without irreparable injury to adjacent normal cells. For many squamous cell tumors it ranges from 4,500–5,500 orthovoltage rads, to limited areas (*e.g.*, 5×5 cm.), delivered in about four weeks time—*or the equivalent in dose and time.* Such cancericidal dose-time equivalents, when fairly even fractionation is used, include: about 2,000 rads in one day; 4,000 rads in eight days; and 6,000 rads in thirty-two treatment days.

The main reason for fractionation and protraction of dose is to aid normal tissue recovery; this applies especially to structures such as bone and cartilage.

Dosage alone is not the decisive factor in clinical cure of many localized cancers; histologic and biologic factors are more important. Glücksmann and Cherry[14] in a study of 615 cases of cervix cancer found the optimal range to be from 6,000–7,000 combined orthovoltage and gamma r in the paracervical tissues at point A. For Stages I and II the greatest five year survival rate was found in the lowest dose range.

INDICATIONS FOR DIFFERENT VOLTAGES

The radiologist is concerned with the deliverance of an adequate dose of ionizing radiation to the tissue of interest, with maximum possible safety to adjacent normal structures. The dose may be delivered by widely different beams and devices, depending on the equipment at hand, the skill and experience of the therapist, the location of the tumor, the status of the overlying or adjacent tissues, and other matters.

In general, most superficial lesions (skin or lip) can be effectively treated with "low voltage" roentgen-ray units operating at

50–150 kvp. When such lesions infiltrate deeply (*e.g.*, extensive skin carcinoma of the inner canthus region), they are no longer superficial and more penetrating radiation will tend to result in more homogeneous ionization of the tumor. Still deeper lesions can be effectively treated with "orthovoltage" units in most instances—combined with intracavitary or interstitial radium or radioactive cobalt in selected sites such as uterus, tongue and maxillary antrum. With these units one can readily deliver more radiation than the normal deep structures will tolerate. Simon and Silverstone[37] write: "The increase in depth dose with cobalt 60 teletherapy is too often considered to be the major advantage of this form of therapy, although there are no deep seated lesions which cannot receive a cancericidal dose with 200 kv. radiation with multiple fields. . . . We are limited in dosage of deep seated lesions by the radiosensitivity of adjacent organs, not by the lack of penetrability of our rays."

Then why megavoltage? Because in selected cases such as very thick or obese persons, or rare circumscribed tumors unsuited for radical surgery such as retinoblastoma in a remaining eye, the physical property of the harder beam may permit more effective irradiation. Also in persons with tumors situated beneath skin badly damaged by prior disease or injury, the initial skin-sparing effect of megavoltage will usually permit more effective treatment.

When delivered with megavoltage beams, a larger physical dose must be used for a given biologic effect. The factor varies and is indicated by approximate figures in Table 1. In general, and with all other technical factors (such as distance, field size, fractionation and associated matters) remaining the same, one needs from 20 to 30 per cent more administered physical dose in megavoltage rads to equate a given biologic effect of orthovoltage rads. This fact, though known for several decades, is often not appreciated.[10] When it is, increase in radiation comfort with megavoltage often proves evanescent.

ADVANTAGES OF MEGAVOLTAGE

The relative advantages of megavoltage have been described under the following headings: 1. Increased depth dose. 2. Diminished skin dose. 3. Decreased bone dose. 4. Greater patient comfort. 5. Better results.

1. *Increased Depth Dose.* This is more correctly expressed as "increased *physical* depth dose." When allowance is made for the decreased biologic efficiency of megavoltage beams, it is found that for many *clinical* situations the biologically effective depth base is little greater than with orthovoltage.

Opposing fixed beams provide the most accurate way of "cross firing" or dosing deep-seated tumors. When nonopposing or oblique fields are used, the tumor may be incorrectly centered and therefore partly underdosed. When rotation therapy is used, the volume usually requiring treatment tends to result in undesirable general reactions, except in selected cases of cancer of the esophagus—and even in this site, the clinical results of rotation therapy leave much to be desired.

Opposing fields present a limitation for megavoltage beams because of the increased dose at the far side of the patient (the exit dose). This automatically limits the amount that can be given to each field with safety, and tends to offset the advantage of increased penetration. The matter is illustrated by considering a small mid-pelvic tumor which is to be treated in conjunction with intracavitary radium (Fig. 1). Let us assume an average patient of 20 cm. thickness. Since megavoltage (in this case telecobalt) produces maximum ionization beneath the skin, and orthovoltage does so in the skin itself, these two zones require separate consideration as far as tolerance is concerned. Let us assume conventional orthovoltage factors of 200 kvp., HVL 1 mm. copper, target-skin distance of 80 cm., and

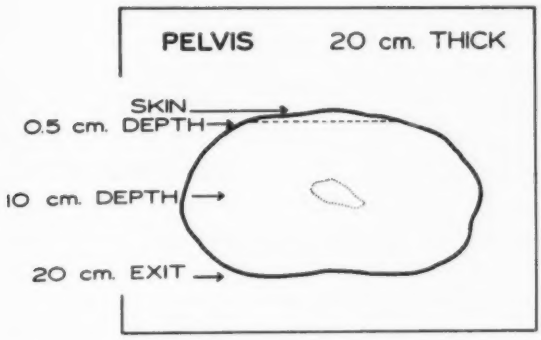

Fig. 1. Diagram of cross section of pelvis, with dotted outline of theoretical tumor in mid-portion.

field size 10×10 cm; the telecobalt factors include HVL 14 mm. copper, source-skin distance of 50 cm., and field size 10×10 cm. The diagrams (Fig. 2 to 4) show that with two opposing beams one needs with megavoltage a smaller skin dose, but *a higher subcutaneous tissue dose* to deliver biologically equivalent doses of radiation to the midpelvis. The 10×10 cm. field size is used so as to give the advantage to megavoltage. The relative improvement in midplane depth dose with megavoltage is about 65 per cent with 10×10 cm. beams, but only about 25 per cent with 20×20 cm. fields. The latter are often necessary in clinical cancer treatment, and of course further decrease the comparative value of megavoltage.

The diagrams show that a subcutaneous dose of 5,000 mv. rads is reached under the conditions described. This dose, delivered in 4 weeks, is apt to be followed by *late* fibrosis and other undesirable reactions, which tend to offset the *early* gain of decreased skin reaction.

To avoid cross firing the same subcutaneous area, 3 nonopposing fixed beams, or a rotating beam, are often employed. The three nonopposed fields may be an anterior one and two oblique posterior fields; the rotation beam may consist of a 260 degree arc. Data from Chamberlain[5] show that

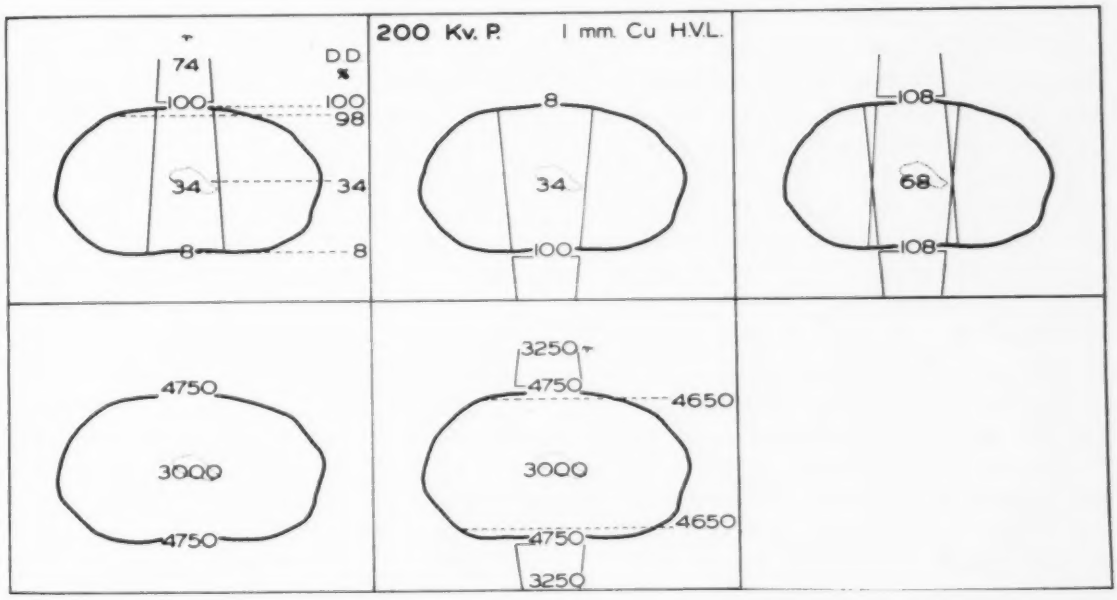

Fig. 2. Diagrams showing depth doses with orthovoltage therapy (200 kv.), half value layer 1 mm. copper 80 cm. target skin distance, field 10×10 cm., pelvis 20 cm. thick. Note that for 74 r delivered in air to an anterior field, there is a skin dose of approximately 100 r, a 10 cm. depth dose of 34 r, and an exit dose of 8 r. Accordingly, to deliver 3,000 r to a hypothetical tumor in the mid-pelvis via 2 opposing small fields of this type, one will deliver about 4,400 r to the skin of an anterior pelvic field and 4,400 r to the skin of a posterior pelvic field. With exit dose added, each skin field receives about 4,750 r. The approximate dose at 0.5 cm. beneath either of these fields is 4,560 r.

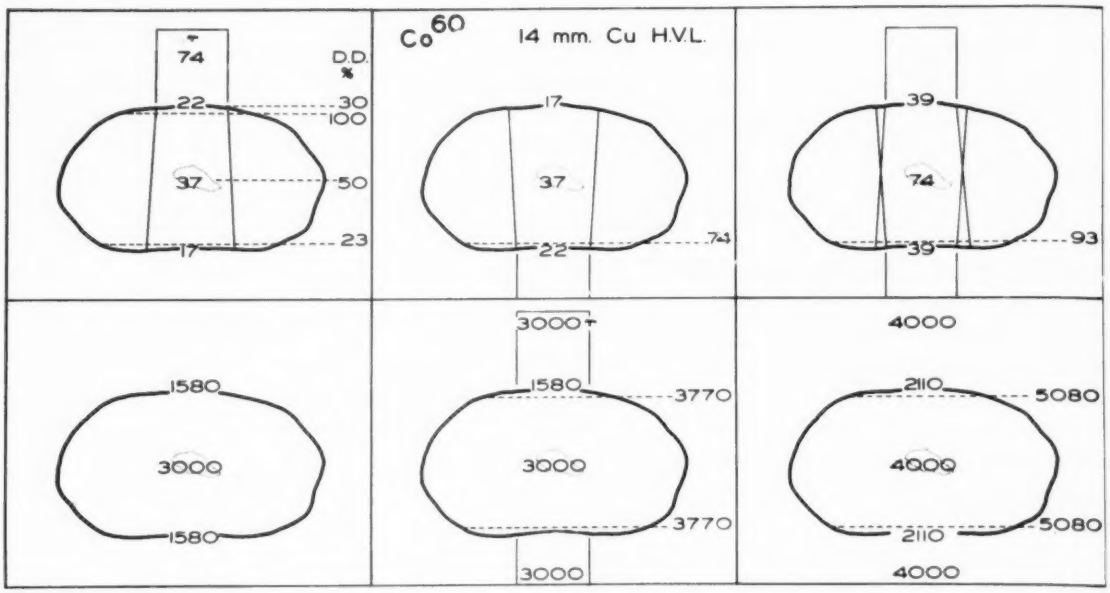

FIG. 3. Diagrams showing depth doses with 1,200 curie Co^{60} unit, half value layer 14 mm. copper, 50 cm. target skin distance, field 10×10 cm., pelvis 20 cm. thick. The skin dose is proportionately much less than that delivered with orthovoltage rays, but the subcutaneous tissue dose is slightly larger, if biologically equivalent doses are delivered to the mid-pelvis. The optimal low backscatter figure of 30 per cent is used; megavoltage beams of other types and size may result in 60 per cent skin dose.

either of these techniques does yield relatively improved *physical* depth dose with megavoltage. With megavoltage double arc rotation, the same tumor depth dose can be attained as with telecobalt rotation or three fields of 4 mev., *but there is a greater volume of nontumor tissue irradiated.* When allowance is made for the decreased biologic effectiveness of supervoltage radiation, the "250 kv. curve is appreciably close to the supervoltage ones." In other words, there is little or no significant increase in biologically effective depth dose with megavoltage under many ordinary clinical situations.

The shielding effect of bone with orthovoltage should and can be allowed for. With small beams (8×12 cm.) it can amount to about 20 per cent in the case of tissues underlying the sacrum or the thoracic spine. Conversely, the radiotransparency of the lung should be compensated for

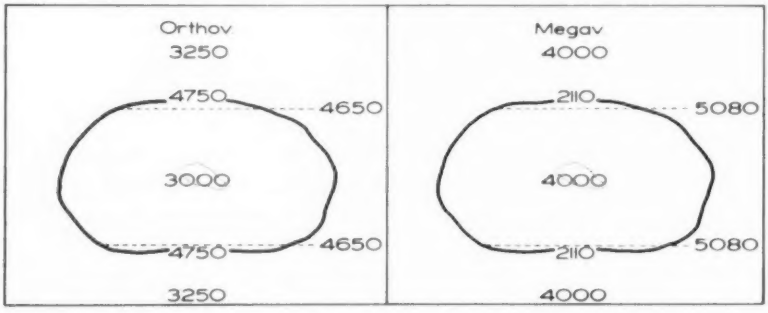

FIG. 4. Diagrams summarizing findings of Figures 2 and 3. The subcutaneous dose with cobalt 60 is actually larger than that with 200 kv. roentgen rays to attain biologically equal depth doses under the specific conditions described, that is 5,080 rads instead of 4,650 rads.

(it permits about 20 per cent more transmission than solid tissue). Neither physical feature limits effective orthovoltage therapy in clinical practice.

2. *Diminished Skin Dose.* This real property of megavoltage, often considered an advantage, is frequently the contrary. Skin erythema is a useful and readily visible indicator of, or clue to, deeper tissue tolerance. When there is a warning skin reaction, dosage can be reduced, protracted or terminated, and important deeper structures thereby protected. Serious and disabling late subcutaneous fibrosis, nerve damage, pulmonary fibrosis, gastrointestinal tract injury and perforation have been reported not infrequently following supervoltage therapy, despite an intervening relatively intact skin.

For persons of average build, skin tolerance is *not* the limiting factor in radiation therapy, but rather intestinal, bronchial and neural tissue tolerance.

Early skin reaction under radical radiation therapy will be more severe with orthovoltage, but late changes tend to be about equal—with subcutaneous injury added to the megavoltage dermal changes.[3,31]

3. *Decreased Bone Dose.* When physical measurements are made under laboratory conditions, the absorbed dose in *compact* bone is found to be about unity with megavoltage beams (as compared with a factor of 2 with orthovoltage). In other words 600 megavoltage r in compact bone yields about 600 megavolt rads, while 600 orthovoltage r yields about 1,200 rads. The physical dose in the adjoining *cancellous* bone and *bone marrow* is estimated as being about equivalent in terms of physical rads; the biologic dose is different by the previously mentioned factor of approximately 0.8. In *clinical* practice, Friedman *et al.*,[8] Schulz[35] and others[12,22] report that the incidence of bone necrosis with supervoltage therapy is similar to that from orthovoltage. Friedman *et al.* believe that "anatomic, clinical and pathologic factors contribute much more to the production of radionecrosis than the physical factors." Simon and Silverstone [37] report that "radionecrosis of the jaw has been observed after cobalt 60 and other forms of supervoltage irradiation, and may even increase in incidence because of our tendency to give larger doses when using supervoltage."

4. *Greater Patient Comfort.* Of all the intangibles in radiation therapy, this is one of the greatest. When large fields are employed and dosage is protracted in the manner often required in clinical cancer radiation therapy, it is usually found that there is as much nausea, vomiting, diarrhea and malaise with supervoltage as with orthovoltage therapy, when biologically equivalent doses are delivered. However, with small fields, and only physically equivalent doses, there is relatively less volume of tissue irradiated and less immediate skin reaction with supervoltage therapy; the smaller biologic dose naturally aids increased comfort, but results in inadequate therapeutic outcome.

We have seen many patients with decreased comfort following supervoltage treatment because of persistent neutropenia, late subcutaneous tissue damage, intestinal injury and bone necrosis. In general, megavoltage effects parallel orthovoltage reactions when equally large biologic doses are given.

By proper graduation of dose and suitable medical attention, patient comfort can be as readily assured with orthovoltage therapy as with megavoltage. When large fields must be used (*e.g.*, with ovarian carcinoma) patients may incur side effects with either voltage. In clinical practice, the virtue of the decreased volume or integral dose that occurs with megavoltage is seldom a major factor.

5. *Better Results.* There is no valid statistical evidence of improved cancer palliation or cure rates to date. Cancers of the uterus, esophagus and lung have not yielded better results with supervoltage therapy than with orthovoltage (Philips,[31] Buschke,[2] del Regato and Regaud,[6] Jacox,[16] Martin[23]). Even bladder cancer has proved disappointing (Friedman *et al.*,[9] Pointon[32]).

Comparative five year data will be found in the next section.

COMPARATIVE RESULTS

Valid comparison of results in cancer therapy is difficult because of differences in grading, staging and associated clinical care of two given groups of cases. However, when the two groups are from the same institution, of the same general type and stage, and cared for during a given decade by physicians of equal training and experience, comparison has some validity. Much of the following data is chosen for that reason.

A. HEAD AND NECK TUMORS

Larynx: Cantril[3] found no improvement in five year cure rates of larynx cancer with supervoltage therapy. His rates were 55 per cent with orthovoltage and 41 per cent with supervoltage therapy (20 and 36 cases, respectively). He noted that comparable series of patients treated at the University of California Hospital showed no difference—63 per cent five year arrests in each group (44 and 46 cases, respectively, in the orthovoltage and supervoltage groups). He wrote "one comes to the conclusion that in radiotherapy the quality of the radiologist and not that of the rays is the deciding factor . . . from evaluation of patients treated by others plus our own results, supervoltage roentgen rays or telecobalt would not appear to be an important factor."

Friedman, Southard and Ellett[8] write "For many lesions, supervoltage roentgen rays have been disappointing and it is probably preferable to use orthovoltage and interstitial radium." It is easy to irradiate the head and neck with supervoltage, but there is not an accompanying significant improvement in the arrest rate of such cancers. Indeed, "our previous experience with 250 kv. roentgen rays in the treatment of parotid cancers has been more favorable than with supervoltage irradiation."

Fletcher *et al.*,[7] Jacox,[16] Lampe,[20] Lenz,[21] Moss,[24] and Nickson[27] also find no statistically valid evidence of better results in laryngeal cancer with supervoltage therapy.

Our own experience with laryngeal cancers includes some 175 patients, treated by orthovoltage roentgen therapy. The majority of these were intrinsic squamous cell carcinomas (Fig. 5, *A*, *B* and *C*). The five year determinate cure rates in this group are: Stage I (single cord, without fixation), 88 per cent; Stage II (both cords, or single cord with fixation), 79 per cent; and Stage III (one or both cords, with invasion or metastases), 33 per cent.

Some of the radiation failures were successfully treated by subsequent laryngectomy.

The five year cure rate for all intrinsic lesions was 46 per cent; for extrinsic tumors it was considerably less.

Tonsil: Sheline *et al.*[36] report a series of 56 patients treated for cancer of the tonsil; the five year survival rates after orthovoltage therapy were 20 per cent and after megavoltage therapy 20 per cent.

Tapley *et al.*[40] also report a series of tonsil carcinomas treated with both modalities; in 71 male patients the five year survival rates were 21 per cent in each group. They write, "There is no evidence that the form which the radiation therapy of the primary lesion takes (radium alone, radium and roentgen ray, orthovoltage, or supervoltage external therapy alone) has an important effect on the outcome."

Alveolus and Antrum: Paterson[29] reports 42 patients treated with 4 mev. roentgen rays. The two year cures were approximately 42 per cent, "not significantly different from earlier results using 250 to 500 kv. radiation."

B. ESOPHAGUS

Fletcher *et al.*,[7] Friedman,[34] and Philips[31] find no evidence of increased cure rates with supervoltage therapy. Fletcher writes, "Large series of cancers of the esophagus and lung treated with supervoltage have failed to show any appreciable improvement in results when compared with con-

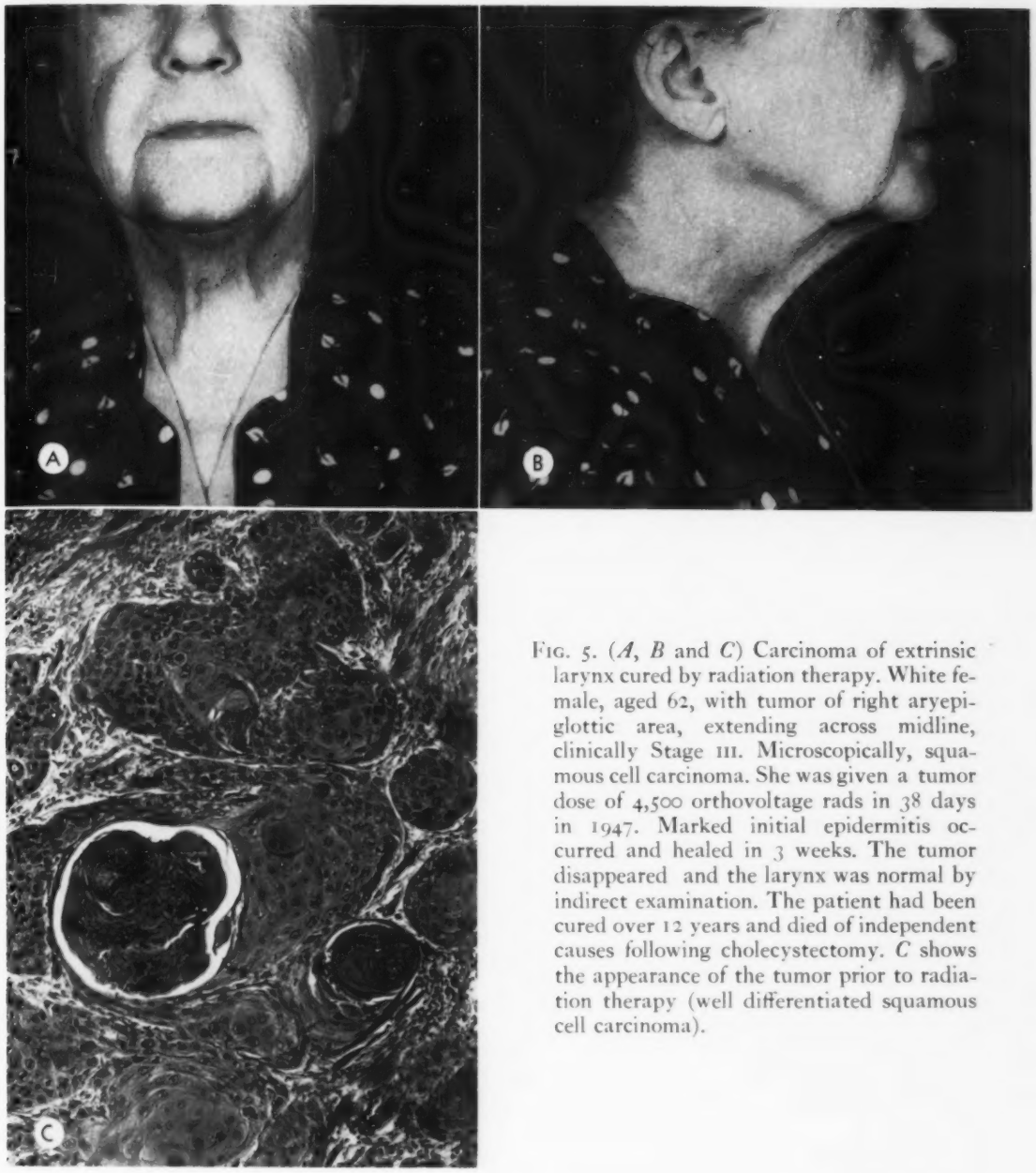

Fig. 5. (*A*, *B* and *C*) Carcinoma of extrinsic larynx cured by radiation therapy. White female, aged 62, with tumor of right aryepiglottic area, extending across midline, clinically Stage III. Microscopically, squamous cell carcinoma. She was given a tumor dose of 4,500 orthovoltage rads in 38 days in 1947. Marked initial epidermitis occurred and healed in 3 weeks. The tumor disappeared and the larynx was normal by indirect examination. The patient had been cured over 12 years and died of independent causes following cholecystectomy. *C* shows the appearance of the tumor prior to radiation therapy (well differentiated squamous cell carcinoma).

ventional therapy, provided that comparable clinical material has been evaluated."

Friedman[34] noted that the first 40 cases of esophageal cancer he treated with supervoltage rotation died within less than two years "which is poorer than several reported groups with 200 kv."

Our experience with esophageal cancer included some 200 patients, treated by orthovoltage roentgen therapy, and a few patients with rotational telecobalt therapy. There are no five year cures. The palliation rate was as good with fixed-field roentgen rays as with rotational cobalt therapy to date.

C. LUNG

Fletcher *et al.*[7] and Philips[31] report no increase in arrests and no significant increase in palliation with supervoltage ther-

apy. Jacox[16] writes ". . . with multimillion volt machines or cobalt beam therapy there has been no significant increase in (lung cancer) cures . . . Nothing can be gained by supervoltage therapy that cannot be obtained by careful planning and treatment application at deep therapy voltages." It is noted that pulmonary reaction and esophageal injury are more apt to occur with supervoltage therapy. Philips[31] reports that "Bronchogenic cancer, like cancer of the esophagus, has proved just as intractable to supervoltage as to medium voltage therapy . . ."

We have reported our experiences with primary bronchial cancer treated by orthovoltage roentgen therapy. Out of some 150 patients there are only 2 five year survivals to date. However, the temporary palliation rate in terms of relief of cough, pain and hemoptysis ranged from 60 to 75 per cent (Fig. 6, *A–D;* and 7, *A* and *B*). Average survival time following radiation therapy was about double that in the untreated group (*i.e.*, 7 versus 3.5 months). Our results with telecobalt therapy to date are not significantly different, the median survival being less than seven months.

D. UTERINE CERVIX

Hunt *et al.*[15] using orthovoltage therapy plus intracavitary radium, report 59 per cent five year absolute arrests in 246 cases. Murphy,[26] using megavoltage therapy plus radium in a series of 1,244 cases, reports 51 per cent five year arrests. If one considers the more localized cases, one finds the following five year arrest figures reported by these authors.

	Stage I (per cent)	Stage II (per cent)	Stage III (per cent)
Orthovoltage Therapy (Hunt *et al.*[15])	87	60	35
Megavoltage Therapy (Murphy[26])	75	55	36

These data show no increase in cure rate in cervical cancer with megavoltage therapy.

Stone[38] reported that his five year results in 35 patients treated with 200 kv. were superior to those in 35 comparable cases treated with 1,000 kv. roentgen rays.

We have treated several hundred patients with cervix cancer using a combination of radium and orthovoltage roentgen therapy. In recent years our five year survival rate in treated patients has ranged from 44 to 49 per cent. Except in unusually thick or obese patients, it is not evident that cobalt or megavoltage therapy *per se* will significantly improve these results (Fig. 8, *A* and *B;* 9; and 10, *A* and *B*).

E. OVARY

Cancer of the ovary is difficult to diagnose and to stage; therefore the following figures are reported not as definitive, but as suggestive data. Sisson and Garland, using postoperative orthovoltage wide-field roentgen-ray therapy had 23 per cent five year survivals in 115 cases; Murphy[26] using postoperative supervoltage roentgen rays had 19 per cent survivals in 95 cases—there is of course no significant difference in these figures.

F. BREAST

No writers claim superior results in breast cancer with megavoltage therapy. Indeed, Kaplan and Bagshaw[17] report returning to 140 kv. roentgen rays to irradiate the internal mammary chain; Meurk and Chu[25] report a study of cases treated with 250 kv. and 1,000 kvp., concluding that as far as the chest wall was concerned "the 250 kv. tangential technic delivered the least radiation to the lung." They did however, indicate a personal preference for megavoltage therapy in the supraclavicular area.

Bachman and Macken[1] noted a significant increase in pulmonary fibrosis and pleural reactions with supervoltage-treated breast tumors. They regarded the effusions as being radiogenic in 5 per cent of cases.

For cutaneous lymphatic permeation, orthovoltage would have obvious advantages compared with megavoltage (Fig. 11, *A–D*). However, for the high axillary region in unusually thick patients (especially

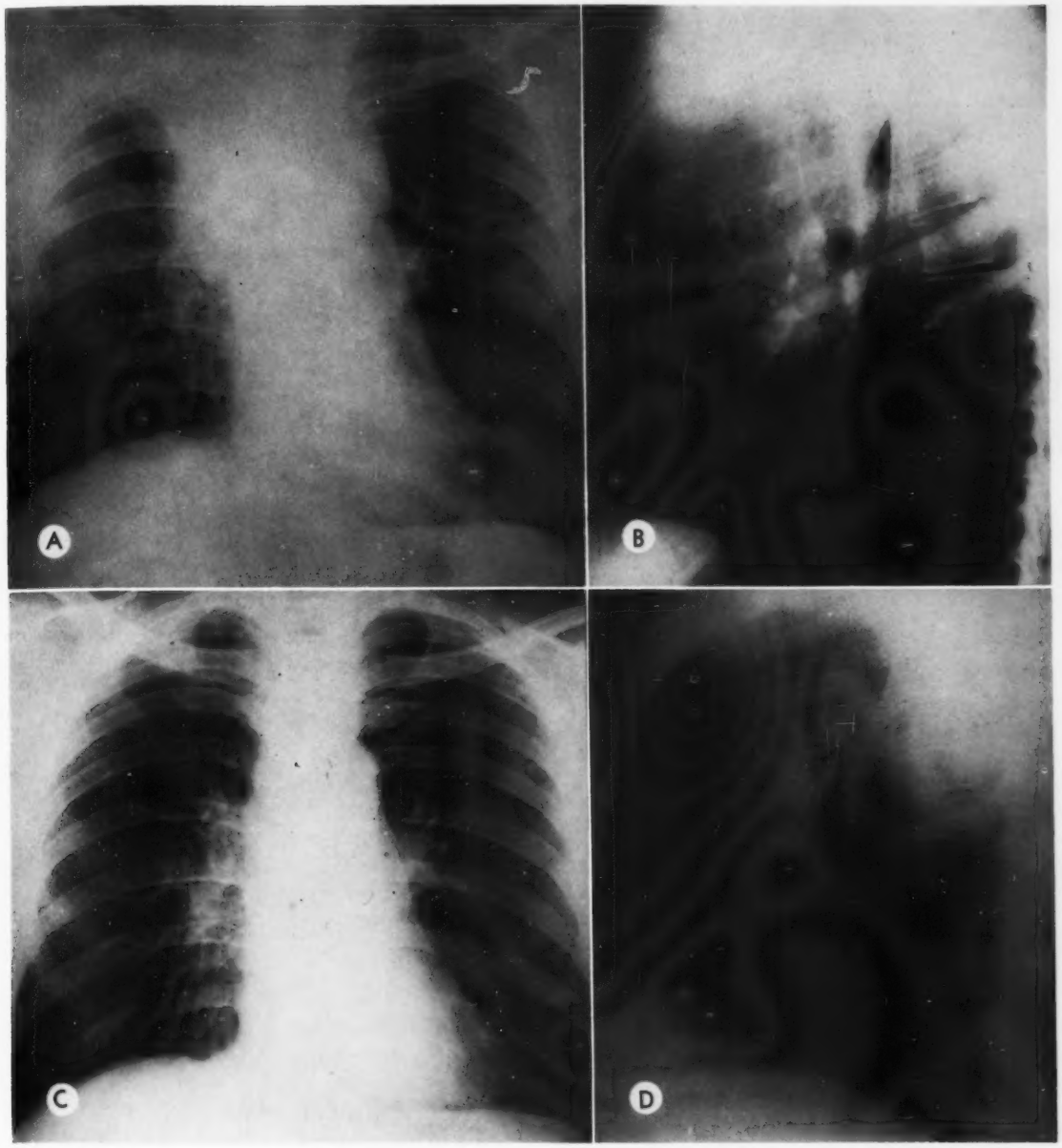

Fig. 6. Primary lung cancer, locally cured by radiation therapy. Male, aged 56, with cough, hemoptysis and weight loss. (*A* and *B*) Roentgenograms show atelectasis of right upper lobe. Bronshoscopy showed a tumor in the right upper lobe bronchus. The carina was fixed and the lesion was regarded as inoperable. Path ologic diagnosis, anaplastic carcinoma. (*C* and *D*) Three months after radiation therapy (3,500 orthovoltage rads tumor dose, in 4 weeks, to an oval area 14 cm. in diameter). The atelectasis has cleared up. The patient returned to work, gained weight and lived for slightly over one year, when he died of cerebral metastases.

in the absence of radical surgery), megavoltage should permit simpler and more effective irradiation.

G. BLADDER

Friedman[9] reports a 13 per cent five year arrest rate in patients treated with megavoltage beams (which he considers much inferior to the 56 per cent rate he previously had obtained with intracavitary radioactive sources).

Paterson[29] and Pointon[32] report results of

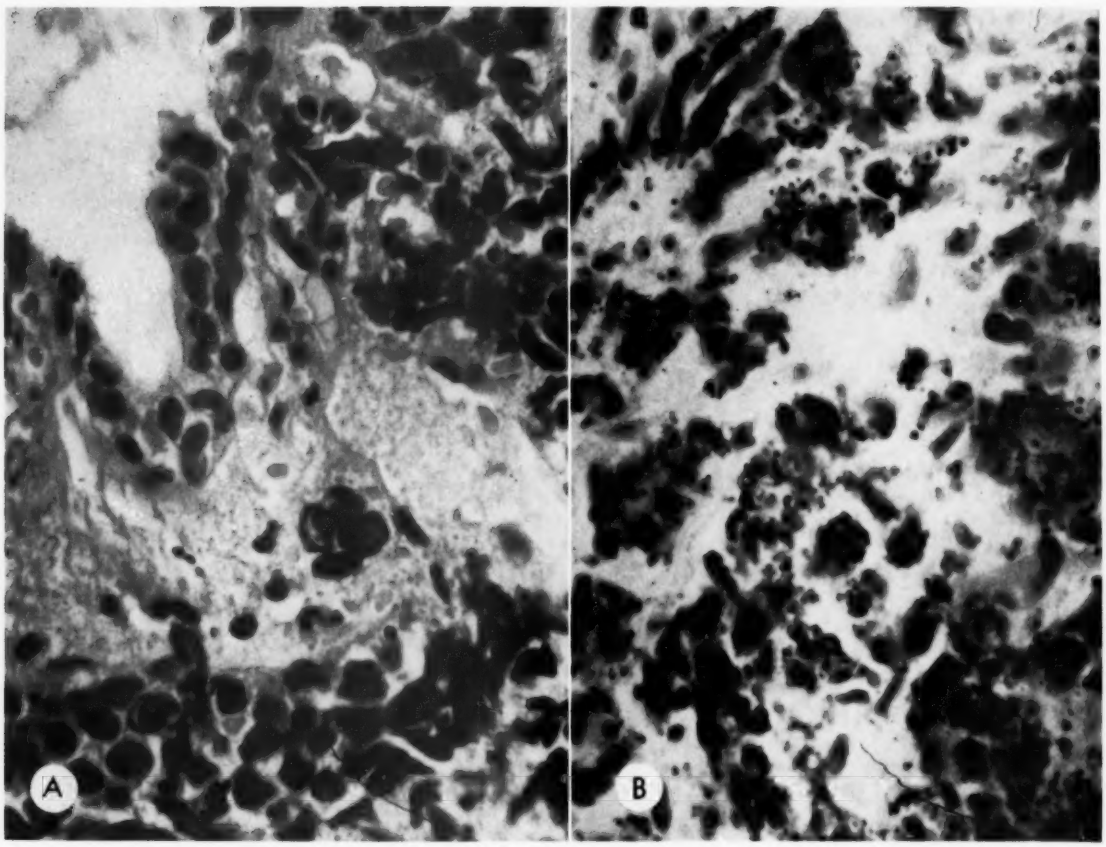

Fig. 7. Same patient as shown in Figure 6. (*A*) Tissue shows epidermoid carcinoma of the right upper lobe bronchus, anaplastic. (*B*) Tissue from same portion of bronchus at autopsy, a little over 12 months later. There is no microscopic evidence of viable tumor cells in the irradiated area. A minority of epidermoid carcinomas of the bronchus are locally controllable with tissue doses in this range. (Figures 6, *A-D* and 7, *A* and *B* courtesy of Garland and Sisson, *Radiology*.)

radical 4 mev. treatment of 87 patients with bladder cancer. The three year survival rate was 29 per cent—not significantly different from the 27 per cent rate obtained previously with premegavoltage roentgen rays in the 250–500 kv. range.

For localized cancer of the trigonal area, rotation therapy (using orthovoltage or megavoltage) should permit more effective irradiation. We have treated a small number of such patients with a 1,200 curie cobalt rotation unit, with an early tumor response not significantly different from that previously obtained with fixed-field orthovoltage therapy. Other investigators have commented on the relative low radiosensitivity of many bladder cancers—a fact which may explain the disappointing results of megavoltage therapy to date.

H. BRAIN

Peirce[30] reports a twenty year radiation therapy study of over 600 patients with primary neoplasms of the brain and brain stem. Palliation was reportedly good in about three-fourths of the gliomas treated with adequate dosage (about 5,500 orthovoltage rads in seven weeks time); medulloblastomas yielded 20 per cent ten year survivals. He writes: "Supervoltage therapy is not necessary and has no advantage other than some sparing of the radiation dose to the scalp."

Several radiotherapists have used mega-

voltage radiation, with or without rotation, for pituitary adenomas. Their published results are not any better than those obtained with orthovoltage. Using three fields and tumor doses of about 3,000 orthovoltage rads in three to four weeks time, we have treated some 45 cases of pituitary adenoma (mostly chromophobic) with excellent results.

These various data on the relative results actually obtained with orthovoltage and megavoltage radiation (Table II) confirm the observation of Kaplan,[18] published in 1958, that "there has not been any conclusive demonstration that supervolt-

Fig. 9. Roentgenogram of the patient shown in Figure 8 made 7 years after the course of megavoltage radiation therapy shows patchy sclerosis of the sacrum and fifth lumbar vertebra, indicative of radiation osteitis. She had rather severe pain. No clinical or cytologic evidence of recurrent neoplasm was noted.

Fig. 8. (*A* and *B*) Example of skin and subcutaneous tissue changes 7 years after megavoltage radiation therapy. White female, aged 47 in 1952, was treated in that year for Stage II carcinoma of the cervix by 1 mev. roentgen-ray beam, to a dose of approximately 4,000 r in air, to each of 4 fields 8×15 cm. in 29 days and coincidental intracavitary radium therapy. These photographs were made 7 years later. The patient now has marked subcutaneous fibrosis over the pelvis, slight telangiectasis, and painful radiation osteitis of the sacrum and fifth lumbar vertebra.

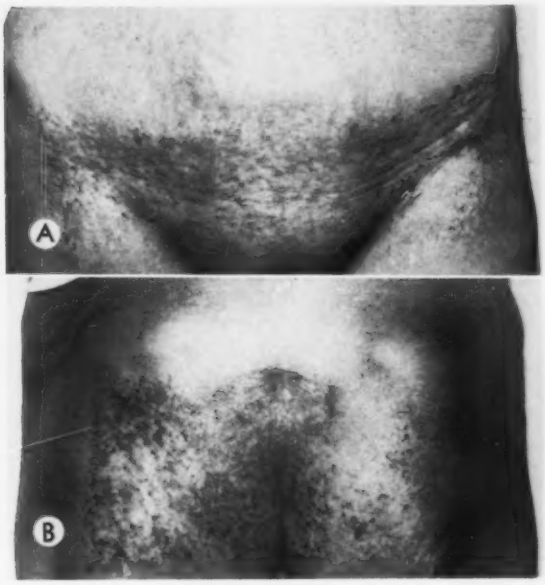

Fig. 10. (*A* and *B*) Example of skin changes 7 years after orthovoltage radiation therapy. White female, aged 49 in 1952, was treated in that year for Stage III carcinoma of cervix by orthovoltage therapy (200 kv., half value layer 2 mm. copper) to a dose of 2,500 r in air to each of 7 fields 10×15 cm. in 46 days. These photographs were made 7 years later. The patient has telangiectasis, but no significant degree of subcutaneous fibrosis, and there is no evidence of radiation osteitis. These skin changes are usually less disabling than the severe subcutaneous fibrotic changes sometimes seen after megavoltage therapy.

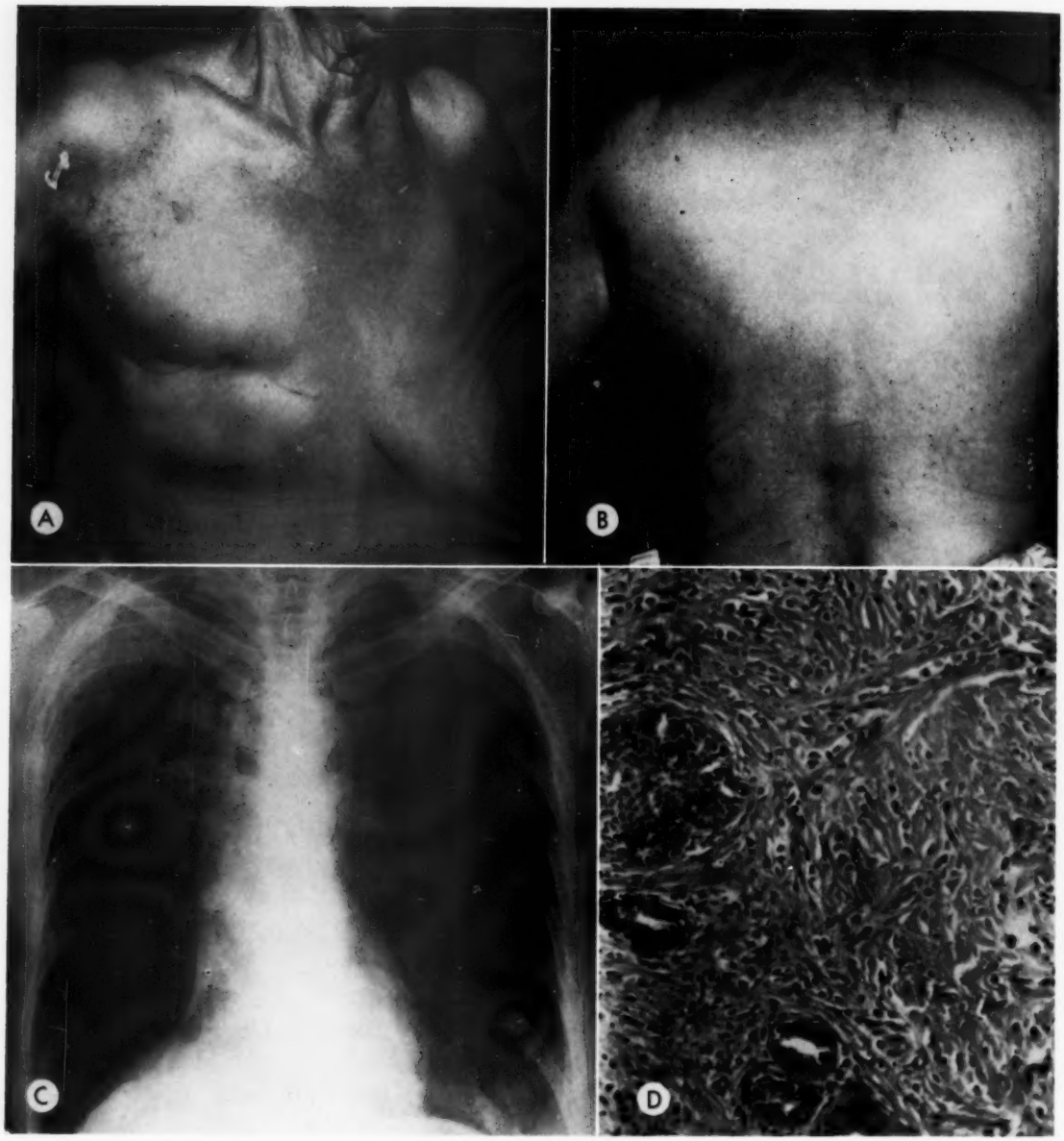

Fig. 11. Mammary carcinoma, locally controlled by simple mastectomy and orthovoltage radiation therapy. Mrs. N. K., aged 57, with Stage 1 carcinoma of right breast treated by simple mastectomy and postoperative radical radiation therapy. (*A* and *B*) Photographs made 5 years after treatment show minimal residual telangiectasis. (*C*) Chest roentgenogram 5 years after treatment shows no pulmonary fibrosis. (*D*) Histologic appearance of primary tumor (adenocarcinoma) at the time of operation. (Courtesy of *Radiology*.)

age therapy yields a significantly improved cure rate for any particular variety of cancer," and of Martin[23] that "supervoltage machines neither increase the cure rate nor reduce the number of secondary internal sequelae. . . ." Quastler[33] and many others have stressed that the biology of the particular cancer under treatment is the more important factor.

COMPLICATIONS

The complications of radiation therapy may be listed as early and late, local and general. They include erythema, telangi-

Table II

SUMMARY OF COMPARABLE CLINICAL RESULTS WITH ORTHOVOLTAGE AND MEGAVOLTAGE THERAPY

Author	Tumor Site	Orthovoltage Therapy (200–400 kv.) (per cent*)	Megavoltage Therapy (1,000–6,000 kv.) (per cent*)
Cantril[3]	Larynx	55	41
Sheline *et al.*[36]	Tonsil	20	20
Friedman[34]	Esophagus	0	0
Philips[31]	Lung	0	0
Hunt *et al.*[15]	Cervix	59	
Murphy[26]	Cervix		51
Pointon[32]	Bladder	27	29

* All data represent five year survival rates except those for the bladder, for which three year survival rates are shown.

ectasis, atrophy, fibrosis, necrosis, pain, nausea, vomiting and even late neoplasia. Fibrosis of deep structures may lead to pericardial, pulmonary, intestinal, neurologic, osseous and other disorders. Necrosis may lead to perforations of hollow viscera, destruction of cartilage or bone, and secondary infections. As with radical curative surgery, a *small* incidence of such complications must be accepted as unavoidable, in the light of the good done the major number. For example, almost 50 per cent of women with uterine cervical cancer (all stages combined) are now curable by effective radiation therapy; the incidence of severe radiation proctitis, ileal fibrosis or femoral neck osteitis is about 4 per cent, or 2 out of every 50 women cured. This compares more than favorably with the complication of ureteral necrosis or obstruction following radical hysterectomy for this disease, reported by its leading proponent as 14 per cent.

Complications must and can be minimized by avoidance of excessive total dosage, and of unduly rapid or intensive dosage. With judicious protraction of treatment, meticulous daily administration and correct associated care, they can be kept to a minimum, whether orthovoltage or megavoltage irradiation is used. However, without care and experience, they are more apt to occur with supervoltage therapy because of the deceptively mild early skin reactions.

Late reactions following supervoltage radiation therapy have been recently reviewed by Leucutia.[22] He writes: "There is accumulating evidence that by using supervoltage radiation therapy . . . indolent fibrosis may be developing in deep seated structures where elastic or areolar connective tissue forms a supporting stroma, and that this indolent fibrosis may be a causative factor . . . accounting for the late changes observed in the parenchyma of an organ or in the basic elements of a system . . . In using supervoltage radiation therapy over the chest, the chances of similar reactive changes are greatly increased." He refers to reports of radiation pneumonitis with fatal outcome, gastrointestinal tract injuries, and urinary tract reactions. He notes the occurrence of radiation myelitis after supervoltage, and the fact that the incidence of radionecrosis of bone and cartilage (following irradiation of head and neck lesions) is similar to that from orthovoltage roentgen therapy.

CHOICE OF MODALITY

Effective radiation therapy requires the deliverance of an adequate but tolerable dose to the diseased area of interest. This may be accomplished by one or a combination of many different modalities. With 200 kv. (orthovoltage) beams, it is possible to deliver such doses to the deeper tissues of most patients without permanent and serious damage to the normal structures near the tumor and without irreparable damage to the overlying skin. Therefore, the radiotolerance of the skin is *not* the limiting factor in deep therapy; it is rather the anatomic extent of the tumor and the relative radiosensitivity of the tumor cells.

For persons who are unusually thick (over 30 cm.) or whose skin overlying the tumor has had serious prior injury, megavoltage beams do have a usefulness by virtue of their better penetration and decreased skin effect, providing nonopposing

fields are used. For rare lesions such as sharply localized posterior retinal tumors, they also have a definite physical advantage. However, in most cases, literal "pin-pointing" of the beam is neither useful nor sensible. "Pin-pointing" of radiation beams has been utilized for four decades, daily in the case of superficial lesions, seldom for deep-seated lesions because their precise anatomic extent is difficult to ascertain, and literal pin-pointing might result in not irradiating large portions of the tumor.

The importance of *visible* biologic reactions is stressed by Glicksman, Chu, Bane and Nickson[13] after a study of patients treated by protracted irradiation: "Experienced radiotherapists will recall patients whose reaction to irradiation systemically or locally was so vigorous as to necessitate termination of treatment after only two-thirds or three-fourths of the usual time-dosage relationship accepted by most patients. In some, the response of the tumor appeared to correlate better with the severity of the biological response than with the physically measured amount of energy delivered to the patient. . . .

"It would appear from the foregoing that a biological triage of responsiveness to ionizing radiation, at least as far as the skin is concerned, does in fact exist. The correlation of these observed classes with other kinds of biological response, *i.e.*, degree of late fibrosis and, perhaps most important, tumor response, must await further studies of these and similarly identified patients. It seems probable that the vigor of reaction of tumor cells to irradiation will be found in the end to correlate more with biological factors than with physical factors."

Orthovoltage beams are regarded as indicated for many if not most patients with neoplastic disease suitable for radiation therapy because with them there is:

(a) *Increased Accuracy of Dose Administration.* Flexible orthovoltage units permit the radiologist to adjust the beam readily to the patient; cumbersome megavoltage units often require adjusting the patient to the beam. Orthovoltage therapy fields can be precisely tailored to the individual case with simple diaphragms or lead sheets; megavoltage units call for cumbersome collimators or lead blocks.

(b) *More Precise Definition of Beam Margin.* Orthovoltage units, when used with cones and skin shields, permit sharp definition of beam edges. Some megavoltage units (notably cobalt and cesium teletherapy units) have ill-defined beam edges owing to large penumbra. Indeed, with small treatment fields, the latter can render the megavoltage device physically less efficient than the orthovoltage unit. There is better protection of normal beam-adjacent structures with many orthovoltage beams. This does not apply to megavoltage roentgen-ray devices utilizing small focal spot tubes.

(c) *Better Protection of Deep Structures.* Skin erythema is a useful clue to tissue tolerance. With warning skin reactions, deep tissues are better protected. Serious late subcutaneous fibrosis, neurologic injury, pulmonary fibrosis and gastrointestinal injury have been reported with megavoltage despite an intact overlying skin. For most persons, skin tolerance is *not* the limiting factor in radiation therapy. With megavoltage, the high exit dose in thin parts such as the neck, may result in excessive dosage.

(d) *Comparable Tolerance.* With orthovoltage radiation, absorption in cancellous bone and bone marrow is closely similar to that from equal doses of megavoltage radiation; however, scatter and presumably absorption in compact bone is greater than that with megavoltage. This last phenomenon may be an advantage and not a disadvantage—for example in treating lesions such as diffuse osseous metastases. The incidence of postradiation osteitis and bone necrosis following radical radiation therapy is apparently about equal with the two modalities, when biologically equal doses are employed.

(e) *Decreased Incidence of Late Subcutaneous Injury.* Orthovoltage beams usually produce maximum ionization in the

skin; after radical therapy there may be late telangiectasis and atrophy. This can be followed carefully, and treated medically or surgically when indicated. Megavoltage beams produce maximum ionization in the subcutaneous tissues (at about 0.5 cm. depth with telecobalt and about 1.5 cm. depth with 4 mev. linear accelerator beams); after radical megavoltage therapy there may be late fibrosis and atrophy of the deep subcutaneous tissues. These are lesions difficult to assess and to treat. If neoplastic change eventuates (*e.g.*, fibrosarcoma), the lesion may be less amenable to cure than an observable skin injury resulting from heavy orthovoltage therapy.

DISCUSSION

In 1932, the roentgen came into general use as a unit of roentgen-ray measurement. Doctors were often impressed to learn that their patient had received a large dose, *e.g.*, 8,000 r. A little inquiry might have elicited the fact that this referred to the air dose of all exposed fields added together—not the actual tumor dose. But the large numbers were impressive to the uninitiated.

In 1933, after trial of a *10 gm. radium bomb* at the Curie Institute, del Regato and Regaud[6] concluded that "it showed no important superiority over lower potential roentgen therapy which was more elastic and less dangerous to all concerned."

Almost thirty years later the same can be said, in general, for cesium units, cobalt units, linear accelerators and multi-million volt roentgen-ray therapy units. But the large numbers—6 million volts, 10 million volts, 90 million volts still impress our colleagues, even though the tumor effect is not increased and indeed the biologic efficiency of the megavolt rad is actually decreased.

In 1938, after several years use of million volt radiations, Stone[39] stated "It is my belief that, with a proper use of 200 kv. radiations, as much effect can be produced in the interior of all but the thickest patients, as their tissues will stand. Progress is to be made not by increasing voltage but by changing such factors as protraction. . . ."

For all accessible, and many nonaccessible, localized radiosensitive tumors, a cancericidal dose can be given with orthovoltage rays. The ease of administration of such dose is enhanced in sites such as cervix, tongue and antrum by associated intracavitary or interstitial gamma-ray therapy. The two agents, orthovoltage roentgen rays and localized gamma rays, constitute the modality of choice in most clinical situations. Nickson,[27] discussing the remarks of Stone and Quastler at the Highland Park Radiation Conference, summarized matters by stating that perhaps the orthovoltage unit "used with care and thought, and used to its limit, may be a lot better than we really think it is." And Constance Wood observed at the 1959 International Radiology Congress that the over-all survival rates with the 8 mev. linear accelerator are not superior to those obtained in a comparable series of cases treated with 250 kv. therapy.

CONCLUSIONS

1. Irradiation of cancers suitable for radiation therapy can be performed effectively with many different modalities—ranging from low voltage roentgen-ray machines to ultra-high voltage electron beam devices, depending on the size, depth, type and location of the tumor and the status of the surrounding tissues. For most deep-seated cancers, patient safety tends to be greater with orthovoltage therapy.

2. The biologic type of the tumor present and the host's defense mechanism are more important than the voltage employed. This has been expressed in the 60–30–10 "law"—which states that the factors influencing the radiologic cure of cancer reside about 60 per cent in the nature and extent of the tumor, about 30 per cent in the skill and experience of the radiologist, and about 10 per cent in the modality employed.

3. There is but little validity to the claim that supervoltage therapy permits an effec-

tive dose with less risk of complications and less general discomfort to the patient (when doses biologically equal to those delivered with orthovoltage rays are used). There may be less initial local cutaneous discomfort with supervoltage therapy, but this tends to be offset by greater ultimate subcutaneous injury.

4. Supervoltage or megavoltage devices may be described as "heavy on promise but light on performance," yet not undeserving of continued scientific investigation under research and preferably controlled conditions—wherein long-term results with human cancer would receive scientific study and deliberate publication.

5. Clinical indications for the use of several types of modality are considered in this paper, and it is shown that, for most neoplastic problems, orthovoltage (200 kv.) roentgen-ray machines plus radium in suitable sources still constitute very effective means of modern radiation therapy.

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This work was aided with funds from the American Cancer Society (California Division), and the Wm. Hume-Albert Barrows Cancer Research Fund.

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ANGIOGRAPHIC HYPERVASCULARITY AND SURVIVAL IN GLIOBLASTOMA MULTIFORME*

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ABUNDANT neoplastic vascularity often is visualized on the cerebral angiogram of a glioblastoma multiforme. In addition to the obvious diagnostic implications in the roentgenographic demonstration of tumor vessels, a richly vascularized glioblastoma provides a clue to a histologic subdivision within the glioblastoma group itself.

In a study of 133 glioblastomas, Busch and Christensen[1] included 74 cases with cerebral angiograms. All but 1 of the 22 tumors with "arteriovenous anastomoses" seen on angiograms were also found to have intense vasculo-proliferative histologic changes (their so-called "angionecrotic" classification). Other investigators have also found parallelism in comparing roentgen and histo-angioarchitecture in this tumor. Cuccia[2] recently considered these features in 59 cases and found that all of the tumors with abundant coarse new vessel formation seen on the cerebral angiogram were likewise highly vascularized on histologic examination, while of the cases with no neoplastic vascularity seen angiographically, 73 per cent showed sparse neovascularity histologically.

A definite parallelism between histologic malignancy and the degree of endothelial hyperplasia in the astrocytoma-glioblastoma group of brain tumors is well recognized and occasionally the hyperplastic endothelial cells in some glioblastomas may themselves assume neoplastic properties and even form sarcomatous tissue.[3] The pathogenetic mechanisms of the peculiar and often bizarre vascular formations observed in glioblastoma are controversial and beyond the scope of this paper.

Since vascular proliferation is intimately related to malignancy in glioblastoma and since there seems to be a correlation between histologic and angiographic studies in vascularization, it follows that the cerebral angiogram *alone* might well be utilized in the analysis of yet another aspect of relative malignancy in this tumor, namely, survival. The purpose of this study is simply to compare angiographic vascularity with longevity in a series of proved cases of glioblastoma.

MATERIAL

Eighty-two cases of histologically proved glioblastoma multiforme with positive cerebral angiograms were reviewed. For simplification, they were separated according to the angiographic findings into two large groups: (1) those demonstrating rich neovascularity in the form of numerous large caliber tumor vessels, "sinusoids," or arteriovenous connections (hypervascular); and (2) those with only relatively few or completely absent tumor vessels (avascular). No attempt was made at further angiographic subdivision, although it is realized that various classifications have been offered, largely for diagnostic purposes.[4,5] The post-operative survival times of each group were recorded and compared.

Twelve patients survived only five post-operative days or less and were rejected as operative deaths. Ten angiograms demonstrated nonfilling, spasm or marked compression of the arterial distribution to the vicinity of the neoplasm and were likewise discarded, since the status of the vascularity within the tumor could hardly be established. Nine cases still living with a post-operative survival time of less than fifteen months were excluded.

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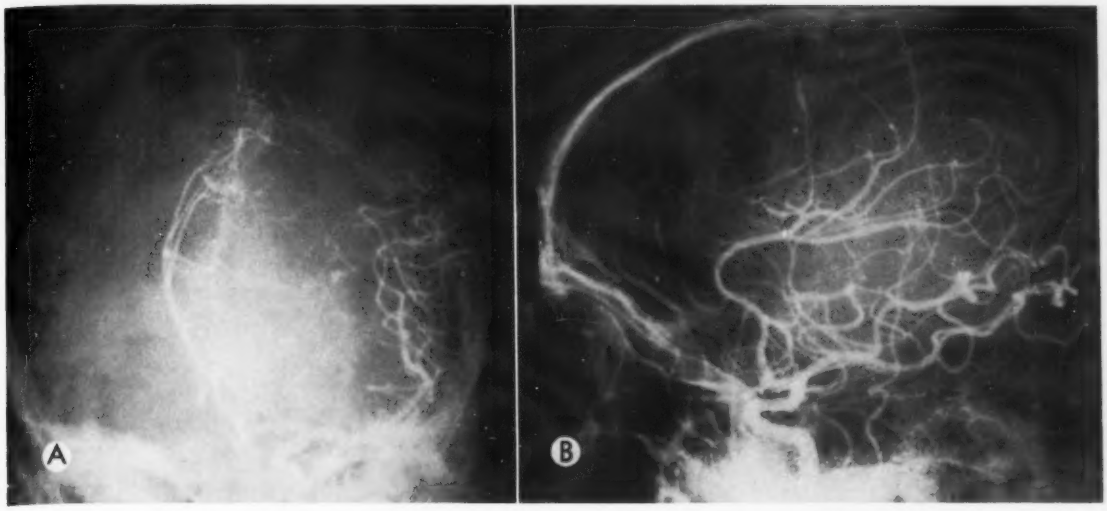

Fig. 1. (*A* and *B*) Avascular glioblastoma in the left frontal lobe. Survival time, thirteen months.

RESULTS

Of the remaining 51 cases with angiograms suitable for this study, 37 cases (72.6 per cent) were found to have scanty or absent vascularity, while 14 cases (27.4 per cent) demonstrated abundant coarse new vessel formation on the angiogram. An example of each angiographic group is presented briefly for illustration.

Case I. P. W., 25358, a forty-three year old Negro male, was admitted with symptoms of three weeks' duration. A left carotid arteriogram revealed a large mass in the left frontal lobe with no appreciable tumor vascularization (Fig. 1, *A* and *B*). A craniotomy the next day was followed by subtotal resection of a large left frontal lobe glioblastoma. The patient expired thirteen months later.

Case II. D. S., E-73716, a forty-seven year old Negro female, developed symptoms five months prior to admission. A left carotid arteriogram demonstrated an extensively vascularized tumor in the left frontal lobe (Fig. 2, *A* and *B*). The same day a glioblastoma was partially resected from the left frontal lobe. The survival time was four post-operative months.

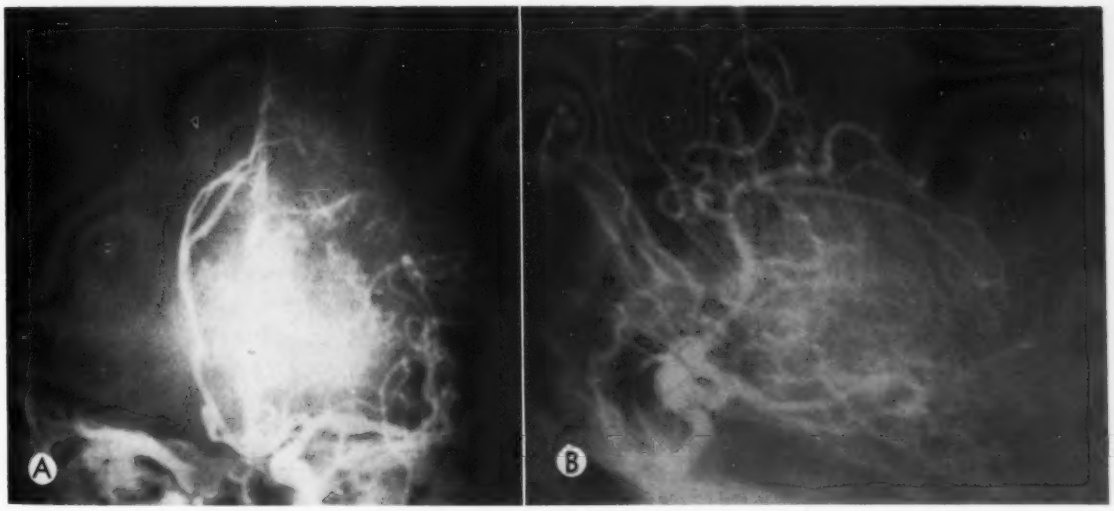

Fig. 2. (*A* and *B*) Hypervascular glioblastoma in the left frontal lobe. Survival time, four months.

Case I represents the angiographically classified avascular glioblastoma, while Case II is a typical example of the hypervascular tumor. Figure 3 charts the percentage survival of each group for the postoperative months survived. These percentages are also compared in Table I. A difference in longevity is apparent with no survivor in the hypervascular group at nine months after surgery. Fourteen per cent of the avascular cases survived one year and 1 patient is still living forty-three months after surgery.

TABLE I

ANGIOGRAPHIC TUMOR VASCULARITY AND SURVIVAL IN 51 GLIOBLASTOMAS

Post-operative Survival (mo.)	Hypervascular Tumors (14 cases)		Avascular Tumors (37 cases)	
	Per Cent Survival	No. of Cases	Per Cent Survival	No. of Cases
3	50	7	81	30
6	29	4	49	18
9		0	24	9
12		0	14	5
15		0	5	2

DISCUSSION

While most of the previous angiographic studies on glioblastoma have concentrated on the diagnostic features of the angioarchitecture, there are few data on an angiographic-survival correlation. The 60 "angionecrotic" cases in Busch and Christensen's[1] series (33 with angiograms) had the poorest comparative prognosis, but the authors did not directly relate the survival data to the angiographic material.

Undoubtedly, some of the avascular cases in this series would have demonstrated tumor vessels at serial angiography and, indeed, delayed exposures have revealed neovascularity in a few of the cases included here. For the purpose of uniformity, the few tumors showing significant new vessel formation only in the "capillary" phase of cerebral circulation are included in the avascular group. The extent of the operative procedures were comparable in the two groups.

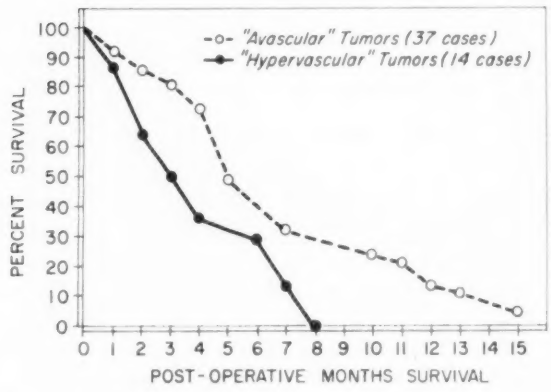

FIG. 3. Angiographically classified tumor vascularity and survival in 51 glioblastomas.

The vascularity-survival data as presented here suggest a malignancy differential in glioblastoma. The results are not intended to accurately represent absolute survival times in cases of this tumor, but only to provide comparative information obtained from two angiographic groupings.

Statistical analysis was not attempted in this small series and any prognostic value of this indication of shorter survival when there is gross angiographic vascularity is obviously limited in the individual patient. The results only emphasize the significance of the angiographic findings when they are considered with the clinical and histologic features of glioblastoma in the study of tumor biology.

SUMMARY

A comparison of cerebral angiograms with survival data in 51 cases of histologically proved glioblastoma multiforme has demonstrated shorter longevity in the group with gross hypervascularity as seen on the angiogram. This supports previous studies on the correlation of histologic malignancy and the intensity of vascular formation in this tumor as well as those stressing the parallelism between its histoangioarchitecture and roentgen angioarchitecture.

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THE ROENTGEN THERAPY OF PONTINE GLIOMAS*

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PONTINE gliomas constitute perhaps 10 to 15 per cent of all brain tumors in childhood. Unfortunately, the vital location of these lesions obviates the possibility of surgical removal. Bailey, Buchanan and Bucy[2] wrote, "until some effective treatment other than surgical is devised, gliomas of the brainstem will be hopeless problems for treatment." Ingraham and Matson,[9] in reporting 30 cases of pontine glioma, felt that some palliation was obtained with radiation therapy. Bray, Carter, and Taveras[5] noted improvement following irradiation in the majority of cases. Bouchard[4] stated that most brainstem lesions are, "radiosensitive to varying degrees." Frequently, the results of irradiation of brain tumors have been analyzed by histologic groups, but not by location, making the value of roentgen therapy for these lesions difficult to determine. This report is an analysis of 42 cases of pontine gliomas seen from 1936 through 1959, with emphasis on the methods and results of roentgen therapy.

CLINICAL FEATURES

Age. The ages in our series ranged from three to fifty-three years. Twenty-nine patients (70 per cent) were in the three through ten age group. Seven patients were over twenty-one years of age. That no patient was less than three years old supports the reported rarity of the lesion before this age.

Race and Sex. There were 24 white patients and 18 Negro patients. Males outnumbered females 23 to 19. No race or sex predominance has been found in the reported cases.

Symptoms and Signs. Most of the cranial nerve nuclei, as well as ascending and descending tracts connecting the cerebrum with the cerebellum and spinal cord, are located in the brainstem. The wide variety of neurologic signs and symptoms which can result from a lesion here might readily be anticipated.

TABLE I

FREQUENCY OF SYMPTOMS IN 42 CASES OF PONTINE GLIOMA

Symptom	No. of Patients
Gait disturbance	28
Dysphagia and dysarthria	20
Diplopia	18
Headache	17
Hemiparesis	16
Nausea and vomiting	16
Facial weakness	9
Dizziness and vertigo	6
Tinnitus and hearing loss	3
Head tilt	2

In contrast to tumors of the cerebellum and fourth ventricle, brainstem gliomas usually show no evidence of increased intracranial pressure until late, if ever.

Headache was the most common *initial* symptom (10 patients), followed by diplopia, abnormal gait and hemiparesis (7 patients each). Facial weakness, nausea and vomiting, dysphagia, dysarthria, and mental changes were less frequently listed as first symptoms.

Gait disturbance was present at some time in well over half the cases. Dysarthria and dysphagia, headache, hemiparesis and diplopia were other frequently noted symptoms (Table 1).

Duration of Symptoms. The duration from onset of symptoms until time of diagnosis ranged from two weeks to three years, 33 cases having had symptoms less than

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Table II

FREQUENCY OF CRANIAL NERVE INVOLVEMENT IN 42 CASES OF PONTINE GLIOMA

Cranial Nerve	No. of Patients
VII	28
VI	24
IX and X	21
V	9
XII	6
XI	3
VIII	3

six months, the remainder from six months to three years.

Neurologic Findings. At the time of diagnosis, cranial nerve involvement was present in all cases with seventh nerve palsy being most common (Table II).

Thirty-six patients had evidence of pyramidal tract involvement such as hemiparesis and Babinski's sign. Papilledema was present at the time of diagnosis in 9 patients. Sensory changes were quite rare in contrast to the multiplicity of motor changes. This observation supports the findings of Bray *et al.*[5]

ROENTGEN FINDINGS

The plain skull roentgenograms were interpreted as abnormal in 13 cases. Separation of sutures was present in 10 cases and increased convolutional markings in 4.

Ventriculography was considered diagnostic of pontine glioma in 18 of 23 cases in which it was performed. Characteristic posterior and upward displacement of the aqueduct and fourth ventricle was described by Lysholm[10] and later by Gardner and Shannon[8] (Fig. 1). In addition, some degree of ventricular dilatation was present in 10 cases.

DIAGNOSIS

The diagnosis of pontine glioma is not, in the majority of cases, based on histologic evidence. Because of the vital structures intimately related to these tumors, there is a high morbidity associated with biopsy. Ingraham and Matson[9] reported that of 21 patients who were explored, a biopsy was possible in only 5.

Fig. 1. Ventriculogram of a five year old Negro male shows characteristic posterior and upward displacement of the aqueduct and the fourth ventricle (verified by operative exploration).

Many patients seen during the first decade of this study did not have ventriculography. This procedure has been a standard part of the diagnostic workup since the late 1940's. Fourteen patients had either no air study or one which was considered nondiagnostic. Each of these patients had sufficiently characteristic clinical findings to justify their inclusion, however (Table III).

Pathologic findings at autopsy revealed 2 cases of glioblastoma multiforme, 2 spongioblastoma and one unclassified glioma. Biopsy was performed in 2 of 8 cases brought to surgery and revealed one oligodendroglioma and one glioblastoma multiforme.

Table III

MEANS BY WHICH DIAGNOSIS WAS ESTABLISHED IN 42 CASES OF PONTINE GLIOMA

	No. of Patients
Ventriculography	18 (3 confirmed at operation)
Operation	5
Autopsy	5
Clinical findings only	14

TABLE IV

SURVIVAL TIMES OF 30 PATIENTS RECEIVING ROENTGEN THERAPY FOR PONTINE GLIOMA

Tumor Dose	Patients		0–3 mo.	3–6 mo.	6 mo.–1 yr.	1–2 yr.	2–3 yr.	3–5 yr.	5 yr.–more
3,000–4,000 r	12	dead	1	3	2				
		living	1		1	2			2
2,000–3,000 r	12	dead	2	1	3	1	1		
		living	2						2
less than 2,000 r	6	dead	3	1	2				
		living							

ROENTGEN THERAPY

Thirty of the 42 cases received at least one course of radiation therapy. All of these were treated with orthovoltage roentgen rays (200–240 kv. peak), with quality varying from 1.1 mm. Cu half value layer to 3.3 mm. Cu half value layer.

In general, three ports were used: two lateral opposing and a single posterior (occipital) port. Fields 6×8 cm. rectangular or 7 cm. diameter circular were commonly employed.

The estimated tumor dose ranged from 1,000 r in two weeks to 4,000 r in four weeks. Most patients treated prior to 1950 received 2,500 r or less in two to three weeks. During the past decade a 3,000–4,000 r tumor dose in three to four weeks has been more commonly administered. The survival times of the 30 treated patients, who were divided into three groups according to the estimated tumor dose, are shown in Table IV.

Although the majority of patients died during the first year following treatment, 4 of 8 living beyond one year have survived five years or more (60, 62, 75 and 117 months; all living and well at the time of last examination). Review of these 4 cases reveals no obvious discrepancies from the typical findings in pontine gliomas. Two diagnoses were confirmed at operation (grossly, no biopsies taken), while the other 2 were established by ventriculography. The patient living and well 62 months after treatment had papilledema and separated sutures at the time of diagnosis, but had a characteristic air study (along with ventricular dilatation) as well as typical clinical features. The nearly normal lives which these 4 patients have enjoyed following therapy is worth emphasizing. The 3 children in the group were reported to be doing well in school, and the forty-one year old patient was leading a productive life when last seen.

The wide range of survival times among similarly treated patients raises the question of the influence of histologic types on prognosis. Ten of Buckley's[6] 25 cases of histologically verified tumors were classified as glioblastoma multiforme and had an average duration from onset of symptoms to death of only four months. Fourteen gliomas were slower growing and classified as protoplasmic or fibrillary astrocytoma or as spongioblastoma unipolare with an average survival of two years. Of the 7 cases with pathologic verification in our series, both the glioblastoma multiforme and the spongioblastoma groups lived less than two months after diagnosis. The single case of oligodendroglioma was living with no evidence of recurrence twenty-six months after receiving 3,500 r tumor dose in a five week treatment period.

TABLE V

CLINICAL RESPONSE OF 30 CASES OF PONTINE GLIOMA AFTER ROENTGEN THERAPY

Improvement following Therapy	No. of Patients
Considerable	12
Moderate	8
Slight or none	10

Any increase in survival time would mean little if not accompanied by remission of symptoms. Many patients responded to a marked degree with an essentially symptom-free interval after therapy (Table v). The degree of response relative to dosage is shown in Table vi.

Reporting definite improvement in 24 of 37 irradiated cases, Bray *et al.*[5] concluded that, "the repeated experience of having induced a clear-cut remission of neurologic symptoms and signs for a short period of time deserves emphasis." Ingraham and Matson[9] likewise felt that radiation therapy was of value in producing decided, though temporary, remissions.

Of 12 patients who received no roentgen therapy, 3 were lost to follow-up and the remaining 9 were dead within two months after diagnosis. These cases cannot serve as a control series, however, as most were not treated because they were considered terminal when first diagnosed.

DISCUSSION

The above data suggest that a tumor dose of less than 3,000 r, and certainly one less than 2,000 r, is below the optimal range. It has been evident from reports in recent years that an upper limit to the desirable dose range also exists. Boden[3] reported 7 patients with various head lesions who developed brainstem damage some months after radiation therapy which included the brainstem in the treatment volume. He felt a reasonable tolerance dose to the brainstem to be 4,500 r in seventeen days (or 5,000 r in thirty days) for a small volume. For a large volume the dose would be 3,500 r in seventeen days (or 4,000 r in thirty days).

TABLE VI

CLINICAL RESPONSE OF 30 CASES OF PONTINE GLIOMA AS RELATED TO THE TUMOR DOSE

Dose	Improvement following Therapy		
	Considerable	Moderate	Slight or none
3,000–4,000 r	6	3	3
2,000–3,000 r	5	3	4
less than 2,000 r	1	2	3

Arnold, Bailey and Harvey[1] reported 2 patients irradiated for brainstem gliomas with tumor doses of 4,500 r in thirty days (400 kv. radiation) in whom radionecrosis of the brainstem appeared after an interval of one year or more. They felt that 3,000 r in four weeks should inhibit tumor growth and not give rise to delayed radionecrosis. Ingraham and Matson[9] used a tumor dose of 3,000 r (treatment time not specified). Bray *et al.*[5] felt 4,000 r in twenty-eight days to be a desirable level. With orthovoltage (200–240 kv. peak) roentgen rays we have delivered 3,500–4,000 r tumor dose in four weeks with no known instances of radionecrosis.

In recent months we have been using higher energy radiation sources such as cobalt 60. The well known skin-sparing and decreased bone absorption effects as well as increased depth dose may prove advantageous in the treatment of these tumors. Because of the evidence of better results with higher tumor doses, 4,500–6,000 r has been delivered with increased protraction and fractionation to avoid radionecrosis.

Attention must be given to the use of sufficiently large fields. The irradiated volume should be generous as many of these tumors extend considerably beyond the pons proper. Buckley[6] found extrapontine extension in 21 of 25 autopsied cases of pontine glioma.

Bouchard,[4] while emphasizing the superiority of a *single* continuous protracted course of treatment, occasionally re-treats a

patient with reactivation if a period of six months has elapsed since the initial treatment *and* if a good response was previously obtained. Bray *et al.*[5] found re-treatment to be valueless if there was no response to the initial therapy. Of 7 re-treated patients in our series, 4 showed improvement (usually less than that following the initial treatment).

Bouchard[4] feels that most brainstem tumors are radiosensitive to varying degrees, although their curability is low, perhaps more because of the vital site of the tumor than because of histologic type. While pontine gliomas may not be radiocurable because of their strategic location and the radiovulnerability of the brainstem, radiation therapy nonetheless plays an important role in the management of these tumors.

CONCLUSIONS

1. Pontine gliomas are most common in childhood and are characterized by multiple cranial nerve and pyramidal tract involvement.

2. The clinical course is usually rapidly progressive, and the majority of patients survive less than one year after diagnosis.

3. Four of 30 patients treated with roentgen therapy survived five years or longer and enjoyed useful active lives.

4. Twenty of 30 treated patients showed definite improvement following roentgen therapy.

5. It is suggested that 4,000 r in four weeks is a desirable tumor dose, using conventional radiation. Below this level response is less frequent and less marked.

6. Higher energy radiation sources such as cobalt 60 along with higher tumor doses (using greater protraction and fractionation) give promise of improved results.

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A SIMPLE PITUITARY LOCALIZER FOR RADIATION THERAPY*

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IT IS desirable, in conventional orthovoltage therapy, to use multiple ports for the treatment of pituitary adenomas to permit delivery of a satisfactory tumor dose without severly compromising the hair, skin, and underlying tissues in the path of any one port. This report describes a simply designed pituitary localizer (Fig. 1) which enables the therapist properly to apply multiple wax seatings to a head cast in such a way that the central ray through each seating will pass through the sella turcica.

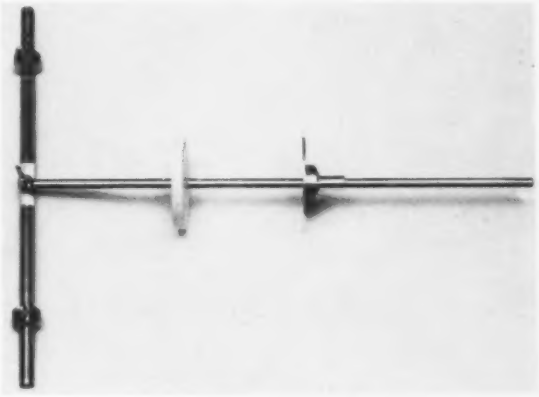

FIG. 1. Pituitary localizer.

The localizer consists of two aluminum rods joined as a T-bar in the center of one, forming a movable angle rule which may be immobilized with a wing nut. The horizontal bar is calibrated in centimeters from the center and extends to 9 cm. to each side. Screw-locking rings aid to center the wing nut in the head cast and lock the horizontal bar in position. The vertical bar is calibrated in centimeters from the wing nut and is marked from 6 to 15 cm. An aluminum disk, 6 cm. in diameter, slides perpendicularly onto the vertical rod. A waxed disk of pliable cardboard is placed between the aluminum disk and the wing nut. The localizer is readily dismantled into its component parts.

The position of the sella turcica is located roentgenographically by adjusting the head in a true lateral position and directing the central ray horizontally through a point 2 cm. anterior to and 2 cm. above the external acoustic meatus. A 5 cm. cone will include a generous area surrounding the sella turcica on the port roentgenogram.

When the lateral position of the sella turcica is ascertained, the point of the central ray on either side of the head is marked. The head cast is then constructed, bringing the plaster of paris somewhat below the marks (Fig. 2). Three additional ports are marked on the outside of the case and cut out with a 2 inch circle cutter. The horizontal rod of the localizer is passed through small side holes, and the wing nut is positioned in the center of the cast by the screw-locking rings. The vertical rod is passed through the open ports and joined to its mate with the washer and wing nut. Warm wax seatings are placed into the open ports (backed by the waxed cardboard) and pressed perpendicular to the vertical rod with the sliding lubricated aluminum disk. When the wax seatings are sufficiently hardened, the localizer is dismantled and removed.

A closed 5 cm. cone applicator is used during therapy. Its end is brought to the wax seatings and positioned perpendicular to the wax surface. The central ray will now replace the position of the vertical bar and will pass through the sella turcica (position of the wing nut), no matter at which position the port was previously marked on

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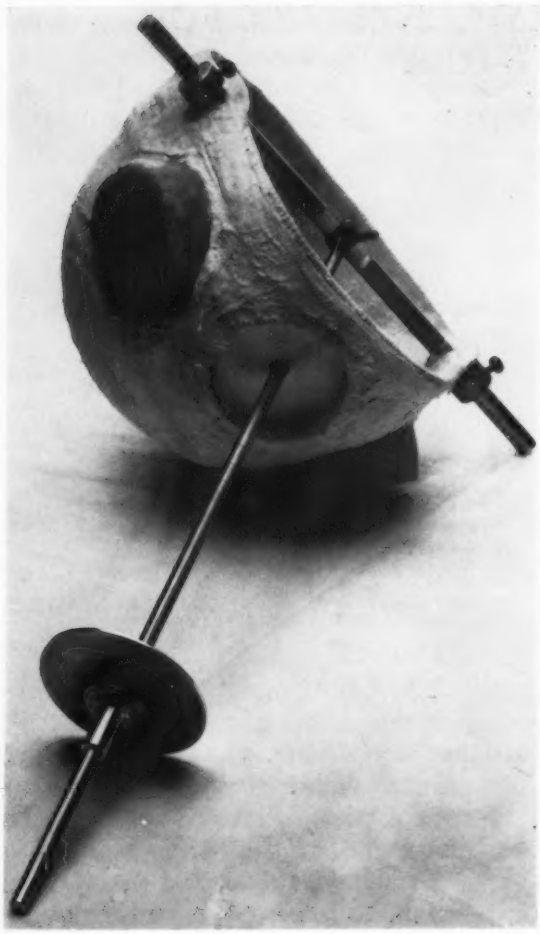

FIG. 2. Position of pituitary localizer in plaster head cast.

the surface of the cast. This has been verified with port localization roentgenograms.

Because the position of the wing nut represents the point at which a predetermined number of ports will intersect within the head, it is therefore possible to use the localizer for lesions which are not necessarily in the median plane. This may be accomplished by placing the wing nut in the general position of the lesion and shifting the screw-locking rings to secure the localizer in the desired position. The subsequent steps to design the head cast and wax seatings remain the same.

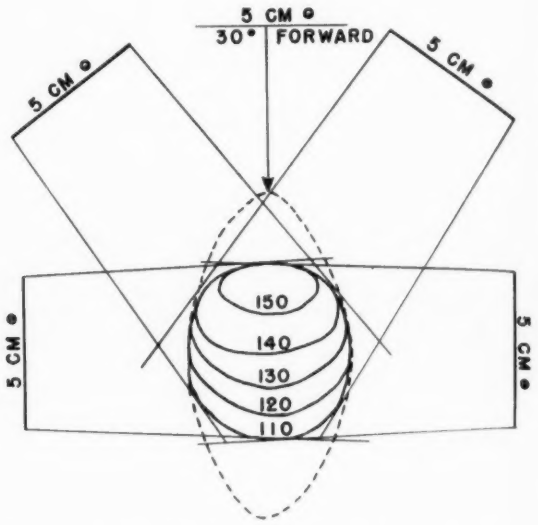

FIG. 3. Isodose distribution utilizing five 5 cm. fields, 250 kvp. deep roentgen-ray therapy unit.

SUMMARY

1. A simple and reliable pituitary localizer for radiation therapy is described.

2. It is used to position multiple ports for treatment of the pituitary gland when a head cast technique is employed.

3. It may be modified to permit direction of the central beam to any small volume within the cranial vault.

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Vol. 86, No. 4

CONTRAST EXAMINATION OF LARYNX AND PHARYNX*

ACCURACY AND VALUE IN DIAGNOSIS

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IF THE treatment of laryngeal or laryngopharyngeal cancer required total laryngectomy regardless of location, size or extent of the tumor, accurate preoperative appraisal of these tumors would be unnecessary. However, with the advent of surgical and radiation therapy procedures by use of which laryngeal function can be preserved in cases of glottic or selected supraglottic and hypopharyngeal tumors, such evaluation becomes mandatory.

A roentgenographic examination proves to be worthwhile only if it can produce consistent and valuable diagnostic information. By contrast roentgenography of the larynx and hypopharynx, tumor masses of these structures can be accurately defined as to location, size and extent. Functional impairment of these structures can be demonstrated. The method is direct, simple, accurate and safe. It can be performed with simple equipment, gives little radiation to the patient and examiner, and takes no more time than a gastrointestinal series. No other method of roentgen examination of this region has been shown to be equally accurate.

Laryngography is not a screening procedure but supplements the otolaryngologist's examination and biopsy. It is more direct and more explicit than laminagraphy or combined laminagraphy and barium swallow studies. No cine-equipment is required to perform a physiologic examination.

Since radiation therapy is the treatment of choice in mobile glottic lesions, a true estimate of mobility and subglottic extent can be graphically recorded by laryngography and glottic lesions can be properly staged. It is also possible by these records to show response of the tumor to irradiation and the functional result after therapy (Fig. 1, *A* and *B*).

TECHNIQUE

The procedure is essentially the same as reported by Powers, McGee and Seaman.[5] The patient is prepared with nembutal and atropine. A topical anesthetic is sprayed into the pharynx and dropped into the larynx. If the patient is in the hospital, 10 per cent cocaine is used; otherwise 1 per cent pontocaine is applied. Ten to twenty cubic centimeters of oily dionosil are dropped slowly over the tongue during quite inspiration. Frontal and lateral spot roentgenograms are made during nasal inspiration, phonation, modified Valsalva and true Valsalva maneuvers. The examination is made before biopsy is done so that edema will not falsely distort the anatomy.

This procedure is not accompanied by any morbidity; rarely, apprehension of the patient prevents the examination from being performed. All of the larynx and hypopharynx can be visualized at one time in one examination. It is direct as opposed to laminagraphy where faulty technique and lack of air contrast may result in errors in interpretation. The method is superior to a barium swallow examination for the hypopharyngeal region where the fleeting passage of the barium bolus is in contrast to the persistence of opacification in laryngograms. Since spot roentgenograms are taken

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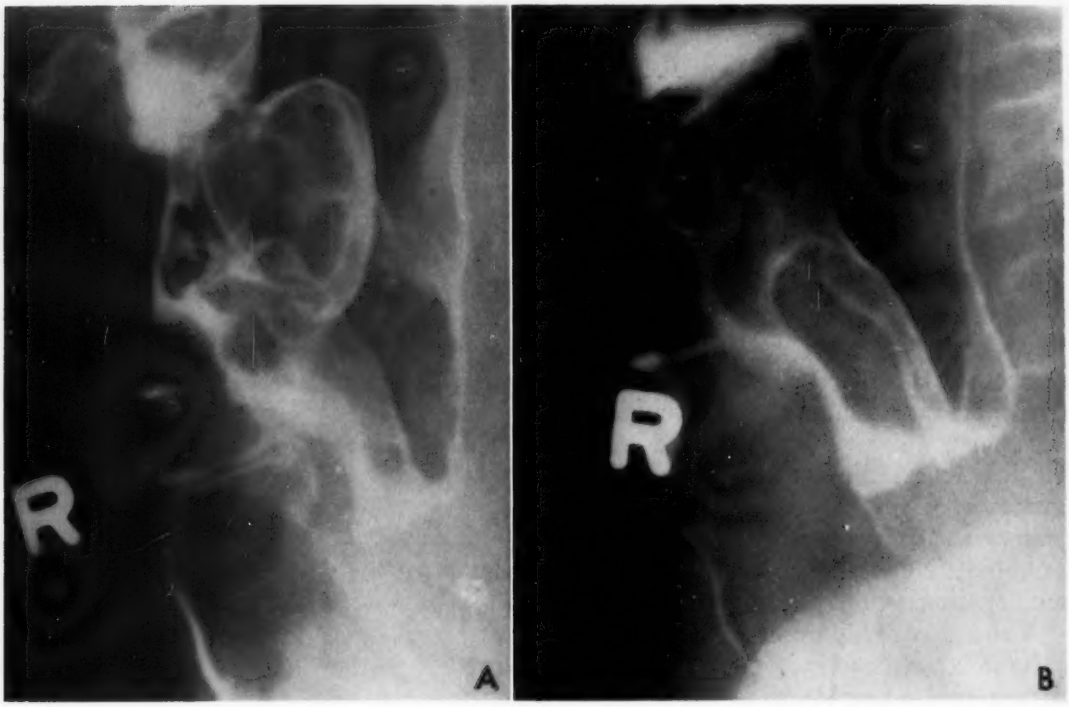

Fig. 1. (*A*) Initial laryngogram revealing a large tumor of the anterior wall of the pyriform sinus. (*B*) Laryngogram four years after therapy demonstrating the response to irradiation with disappearance of the tumor.

at the maximum excursion of the different maneuvers, this is a definite functional examination and in our study the quality of the laryngograms proved superior to that of cineroentgenographic studies.

NORMAL ROENTGEN ANATOMY

All of the structures of the larynx and pharynx are outlined by contrast medium and air. The normal roentgen anatomy has been carefully described in the original article[5] but several points should be reemphasized: (1) in nasal inspiration the cords are retracted and usually not seen (Fig. 2); (2) the true and false cords and vestibule are symmetric (Fig. 3); (3) the angles of the true cord that subtend with the trachea in the frontal and lateral projections are sharp, approaching a right angle; (4) during Valsalva maneuver, air and contrast medium are forced against the undersurface of the true cords, thus accurately defining the beginning of the infraglottic space and any masses that may be present there (Fig. 4); and (5) the lateral wall of the pyriform sinus may be slightly asymmetric, the medial wall usually is not. Lack of change of the pyriform sinus in the different maneuvers indicates infiltration.

CLASSIFICATION AND PATHOLOGIC SIGNIFICANCE OF LOCATION AND SIZE OF THE PRIMARY LESION

Classification of laryngeal lesions differs in various sections of the country and over the world. Recently, McGavran, Bauer and Ogura[1] have reviewed the specimens of laryngeal cancers of cases where *en bloc* total or supraglottic subtotal laryngectomy with incontinuity neck dissection was performed between 1950 and 1959. No case with prior radiation treatment or other surgical intervention has been included. The proposed classification (Fig. 5) based on pathologic data is: (1) glottic—cancers limited to the true cord; (2) infraglottic—cancers of the subglottis and glottis; (3)

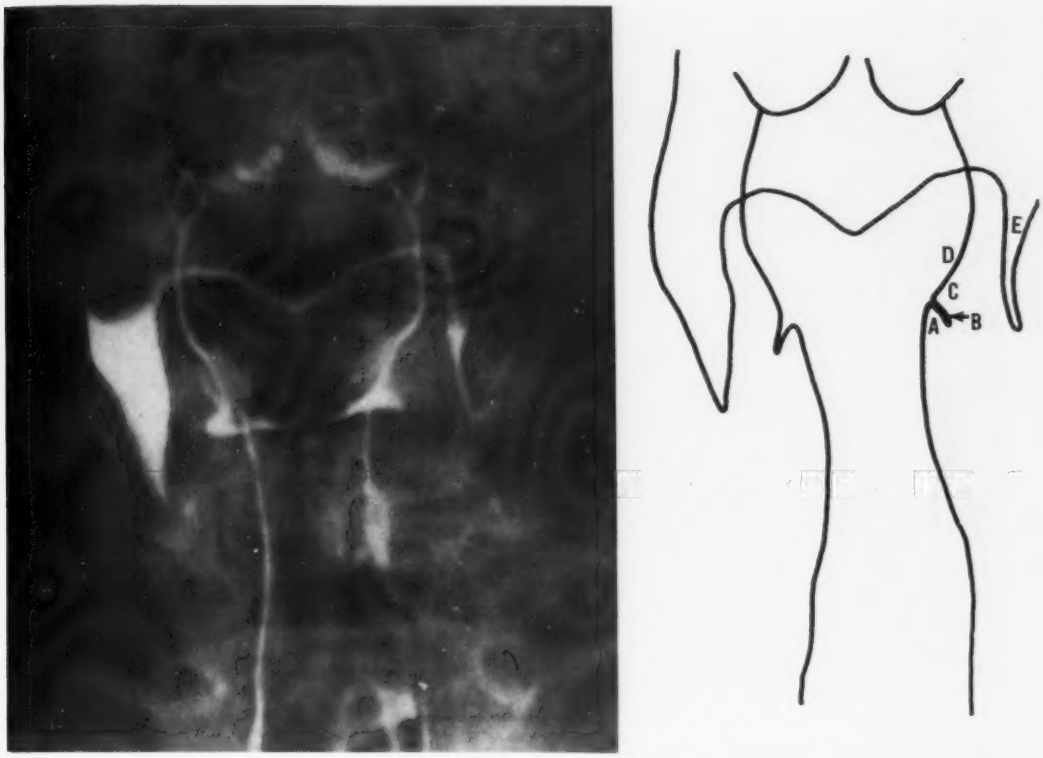

Fig. 2. Laryngogram and tracing showing that the true cords (A) and false cords (C) are retracted with the true cords almost obliterating the ventricle (B). A thin line of contrast material outlines the ventricle, the posterior portion of which lies laterally. The pyriform sinus is seen (E). (Nasal inspiration—frontal view.) (Reproduced by permission from *Radiology*.)

supraglottic—cancers involving the false cord, fixed or free portions of the laryngeal surface of the epiglottis; and (4) transglottic—cancers that cross the ventricle thus involving two or more of the above sites. The rare ventricular tumors are included in this group.

This classification is based on areas of involvement and does not include the hypothetical extrapolation from size and location as to the point of origin. It is based on where tumor is rather than a supposition as to where it began. The glottic, infraglottic and supraglottic types are similar in definition to that used by Pietrantoni and Fior.[4] The value of this classification is the fact that lesions are separated according to the two major divisions of lymphatic drainage.

Of 96 patients studied, it was noted that: (1) there was a progressive increase in metastatic incidence from glottic to infraglottic, to supraglottic to transglottic lesions—0, 19, 33 and 52 per cent, respectively. The metastatic rate of the transglottic group represents the addition of the infraglottic and supraglottic lymphatics, confirming the expected results derived from theoretic considerations of the lymphatic drainage of the larynx (Table I); (2) the transglottic group yielded a higher incidence of both clinically apparent and inapparent metastases. The rate for inapparent metastases for the infraglottic group was 22 per cent, the supraglottic group 4 per cent and the transglottic group 31 per cent (Table II); (3) supraglottic and infraglottic cancers larger than 2 cm. and of moderate or poor differentiation also presented with a high incidence of metastases (15/30) (Table III). Cancers of any size that were well differentiated in these two locations, or

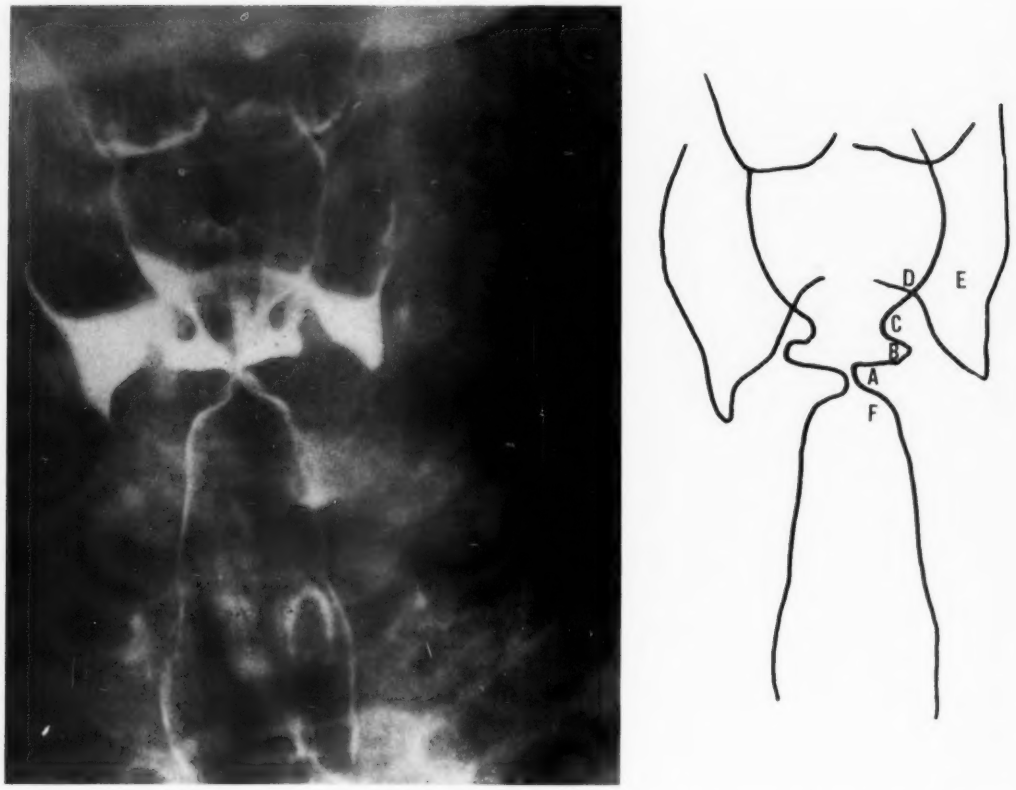

Fig. 3. Laryngogram and tracing showing that the true cords (A), the false cords (C) and vestibule (D) are symmetric. The angle between the true cord and the trachea (infraglottic space—F) is sharp, approaching a right angle. The pyriform sinus (E) has changed in shape from that seen on the inspiration laryngogram. B represents the ventricle. (Phonation—frontal view.) (Reproduced by permission from *Radiology*.)

Fig. 4. Laryngogram and tracing showing air and contrast medium force against the inferior margins of the closed cords (A), which are now in the horizontal position thus accurately defining the infraglottic space (F). (Valsalva maneuver—lateral view.) (Reproduced by permission from *Radiology*.)

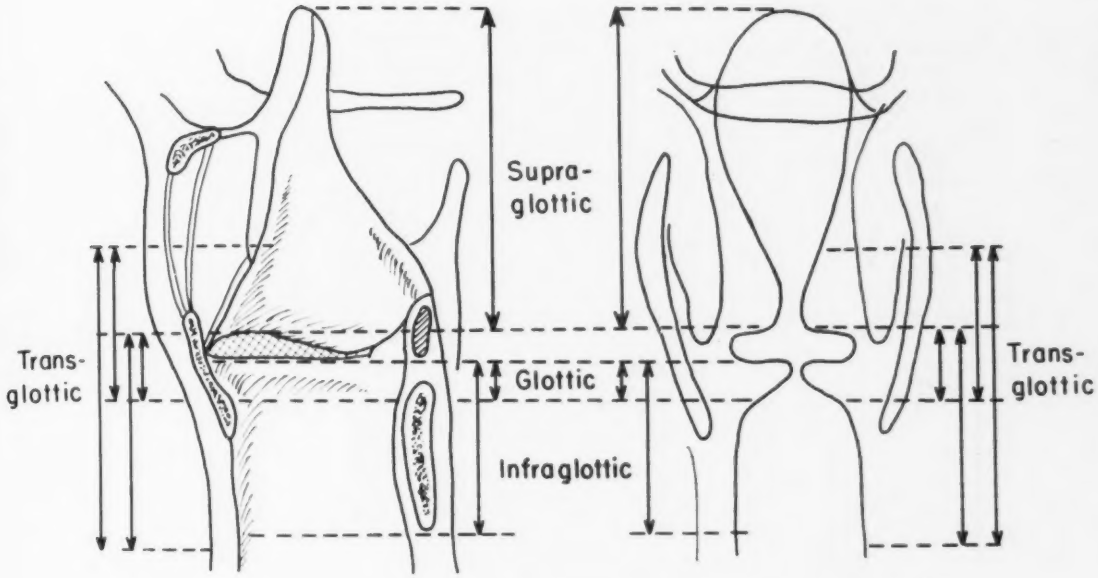

FIG. 5. Diagram showing the classification of laryngeal tumors. (Reproduced by permission from *The Laryngoscope*.)

those of 2 cm. or less and moderately or poorly differentiated, provided a low incidence of metastases to the neck (2/20); (4) of 23 patients with supraglottic or transglottic lesions shown to have cervical lymph node metastases, 48 per cent had proved positive lymph nodes in the contralateral side of the neck on follow-up surgery.

Thus, cases of laryngeal cancer can be separated into groups of high and low metastatic incidence rates by using preoperative information about the site, size and biopsy differentiation of the primary lesion and clinical evaluation of the cervical lymph nodes.

METHOD OF STUDY

Since this study was designed to appraise the diagnostic accuracy of laryngography, it was necessary to document the clinical, roentgenographic and pathologic data separately. This was done on 99 consecutive patients from 1957–1959 who had laryngographies and subsequent surgery, with sur-

TABLE I

METASTATIC INCIDENCE IN 96 CASES OF LARYNGEAL CANCER TREATED BY EN BLOC LARYNGECTOMY AND RADICAL NECK DISSECTION AND ITS RELATIONSHIP TO THE SITE OF LESION
(McGavran *et al.*[3])

Site	No. of Cases	Cases with Positive Lymph Nodes	Per Cent
Glottic	5	0	0
Infraglottic	27	5	19
Supraglottic	39	13	33
Total (a)	71	18	
Transglottic (b)	25	13	52
All Sites	96	31	32

$\chi^2 = 6.02$; p (a) = (b) 0.02.

TABLE II

METASTATIC INCIDENCE IN 68 CASES OF LARYNGEAL CANCER TREATED BY EN BLOC LARYNGECTOMY AND ELECTIVE NECK DISSECTION AND ITS RELATIONSHIP TO THE SITE OF THE LESION
(McGavran *et al.*[3])

Site	No. of Cases	Cases with Positive Lymph Nodes	Per Cent
Glottic	4	0	0
Infraglottic	23	5	22
Supraglottic	25	1	4
Total (a)	52	6	
Transglottic (b)	16	5	31
All Sites	68	11	16

$\chi^2 = 3.5$; p (a) = (b) 0.06.

Table III

SIZE AND CELLULAR DIFFERENTIATION OF THE RESECTED SPECIMEN AND METASTATIC INCIDENCE IN 96 CASES OF LARYNGEAL CARCINOMA TREATED BY EN BLOC LARYNGECTOMY AND RADICAL NECK DISSECTION
(McGavran *et al.*[3])

	No. of Cases	No. of Cases with Metastases	χ^2 P, (a) = (b)
Size			
2 cm. or less (a)	29	4 (14%)	6.5 < 0.02
Larger than 2 cm. (b)	67	27 (40%)	
Differentiation			
Well	9	1 (11%)	
Moderate	46	10 (22%)	
Total (a)	55	11	
Poor (b)	41	20 (49%)	8.9 < 0.01

gical specimens available for comparison. Six of 13 patients with glottic lesions had hemilaryngectomies and the remainder had total or subtotal laryngectomies, all with *en bloc* neck dissection.

The laryngograms were reviewed by the radiologists without regard to previous interpretation and classification or knowledge of clinical data. Noted were: (I) the sites of the lesions (1. glottic; 2. infraglottic; 3. supraglottic; 4. transglottic; and 5. pyriform sinus); (II) the area of involvement (1. the size; 2. the structures involved; 3. whether adjacent structures were invaded or free; 4. the superior-inferior extent of the tumor; 5. the mobility of the cords; 6. involvement of the anterior commissure and across the midline; and 7. involvement of the pyriform sinus, the aryepiglottic fold and the base of the tongue). The cases were then placed into the various classifications. Comments were made as to whether radical excision in supraglottic or pyriform sinus lesions was necessary or whether a "conservation of function" operation could be performed (supraglottic subtotal or transhyoid partial laryngopharyngectomy).

The clinical and direct laryngoscopic observations were then recorded from the hospital records on a master sheet. These findings represented the combined notes of the residents and the attending surgeon and the same criteria for accuracy and error were used as for the evaluation of the laryngograms. Accuracy was verified by correlating the findings with the gross surgical specimens and photographs. Errors were listed whenever the laryngographic interpretations resulted in an erroneous classification.

RESULTS

During the 1957–1959 study period, seven laryngograms made of laryngeal cancer patients were discarded for the following reasons: poor coating, 2 cases; poor quality or insufficient views, 2 cases; edema and distortion as a result of irradiation, 2 cases; and insufficient coating and poor airway in a tracheotomized patient. Four laryngograms could not be located. It was impossible to obtain laryngograms on 2 patients because of uncooperativeness. Laryngograms of 25 other patients were not included since irradiation was the treatment of choice, and therefore no specimen was available for examination. Ten cases had far-advanced cancer and surgery was not considered. Twenty patients with laryngeal cancers underwent surgery without laryngography. In 3 patients laryngograms were made but neither surgery nor roentgen-ray therapy was undertaken. Thus the total number of cases excluded was 71.

The remaining 99 cases of a total of 170 cases of all forms of laryngeal cancer observed during this three year period had a satisfactory evaluation and were used for the present study.

The accuracy of laryngography proved to be high (Table IV), 92 per cent as contrasted to 78 per cent using conventional clinical appraisal. The majority of errors occurred in the infraglottic group. This was due to an enlarged true cord and infraglottic mass (which was fixed most of the time) impressing and almost obliterating the ventricle. Because of the incorrect interpretation of false cord involvement, these cases were classified as transglottic lesions. In only 1 case was infraglottic ex-

TABLE IV

COMPARISON OF THE ACCURACY OF CLINICAL EXAMINATION AND DIRECT LARYNGOSCOPY WITH LARYNGOGRAPHY

Site	Diagnosis	Clinical Examination and Direct Laryngoscopy	Laryngography	Confirmative Surgical Pathology
Glottic	Correct	12	12	13
	Incorrect	1	1	
Infraglottic	Correct	7	9	14
	Incorrect	7	5	
Supraglottic	Correct	22	28	29
	Incorrect	7	1	
Transglottic	Correct	10	16	16
	Incorrect	6	0	
Pyriform Sinus	Correct	26	26	27
	Incorrect	1	1	
Total	Correct	77 } 22%	91 } 8%	—
	Incorrect	22 }	8 }	99

tension missed on the laryngogram. With continued refinement in technique, it should be possible to decrease the error caused by the misinterpretation. Other errors of interpretation were extremely low and are to be expected.

Clinical classification in certain cases of laryngeal and pharyngeal lesions is difficult. Bulky supraglottic tumors are airway problems and the precise lower margins cannot be determined accurately. In this group, freedom of involvement of the true cord can be seen on laryngograms since the lower margins of the neoplasm are defined. Bulky tumors of the false cords that overhang the true cord can also be precisely visualized on laryngograms. Clinically, such tumors are often mistakenly considered to involve the true cord. Tumor crossing the midline was correctly evaluated by laryngography in every case in the supraglottic, infraglottic and transglottic lesions. There was a high accuracy index for pyriform sinus lesions both from the clinical and roentgenographic standpoints.

By laryngography the size of the tumor can be determined for all sites within a mean variation from 0.3–0.6 cm. depending upon the tumor site (Table v), and frequently the actual tumor size can be correlated with the laryngogram. This is impossible by laryngoscopy. The size of tumor, degree of differentiation and location of the lesion have a direct relationship to metastatic spread.

Laryngography was not designed for the appraisal of lesions in the post-cricoid region, and here a barium swallow study becomes necessary. The determination of anterior commissure involvement also is difficult by contrast roentgenography, although suggestive signs may be present.

DISCUSSION

Since 1950 operative procedures less radical than a total laryngectomy have been performed on selected cases at this institution[2] (Fig. 6 and 7). These preserve the cords but are combined with a radical cervical lymph node dissection. The patients have no significant speech disturbance, and are able to swallow without as-

TABLE V

ACTUAL SIZE OF PRIMARY LESION AND LARYNGOGRAPHIC VARIATION

Site	Actual Size	Laryngographic Variation
Glottic	—	—
Infraglottic	1.3–2.6 cm.	±0.3 cm.
Supraglottic	1.0–5.0 cm.	±0.6 cm.
Transglottic	1.8–5.0 cm.	±0.4 cm.
Pyriform Sinus	1.0–6.0 cm.	±0.6 cm.

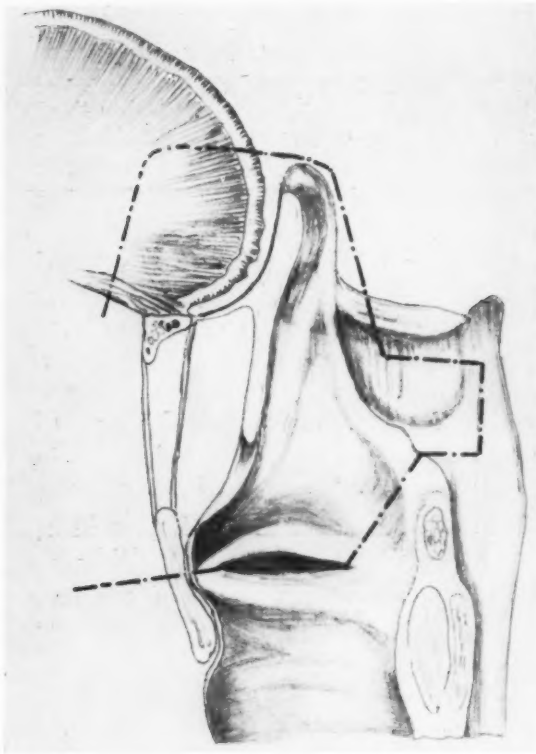

Fig. 6. Drawing showing subtotal supraglottic laryngectomy. The structures enclosed within the interrupted lines are removed, leaving the true cords intact. (Reproduced by permission from *The Laryngoscope.*)

piration (Fig. 8, *A*, *B* and *C*).[3] A one to six year follow-up on these selected cases has shown good results.

The accuracy of the radiologists in classifying supraglottic lesions was high. Out of 17 cases having supraglottic operation, 12 were noted as having wide surgical margins of safety. Examination of the surgical specimens verified this. In 5 cases, where the tumor was in the false cord area, the diagnoses and the extent of the safety margin as evaluated by laryngography correlated well with the findings at surgery. In 6 out of 12 cases in which laryngectomy and neck dissection was performed, laryngograms showed that a supraglottic subtotal operation could have been done. Examination of the surgical specimen confirmed this. The clinical preoperative appraisal was that "there was insufficient margin of safety."

The lymph node metastatic spread is quite dependent upon the location and extent of the primary lesion, its size and degree of differentiation. The time may come when prophylatic neck dissections are abandoned on patients with supraglottic carcinoma, where the metastatic rate of clinically inapparent lymph nodes is low

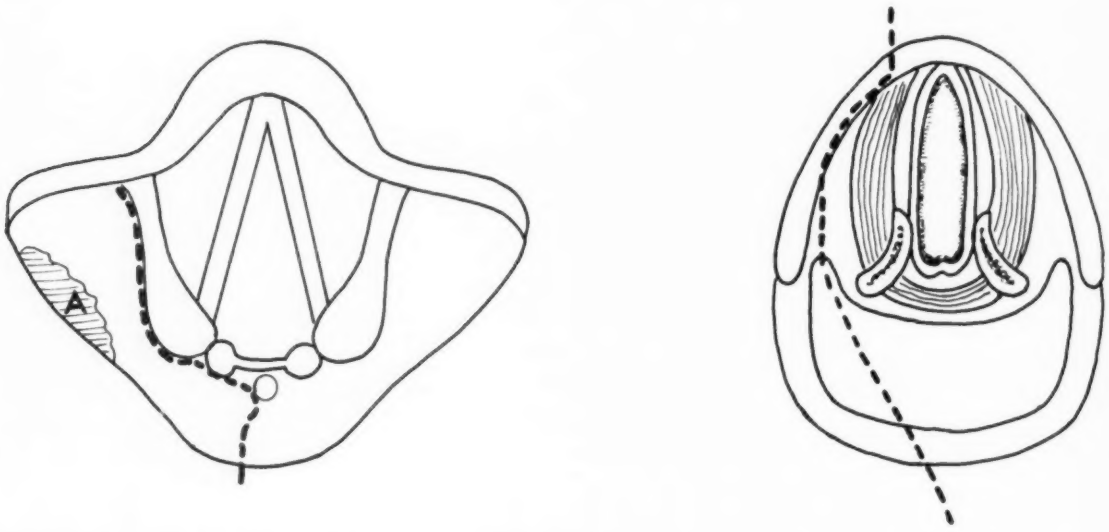

Fig 7. Drawing showing a partial pharyngectomy, by which the tumor on the lateral wall of the pyriform sinus is removed and function is preserved. (Reproduced by permission from *The Laryngoscope.*)

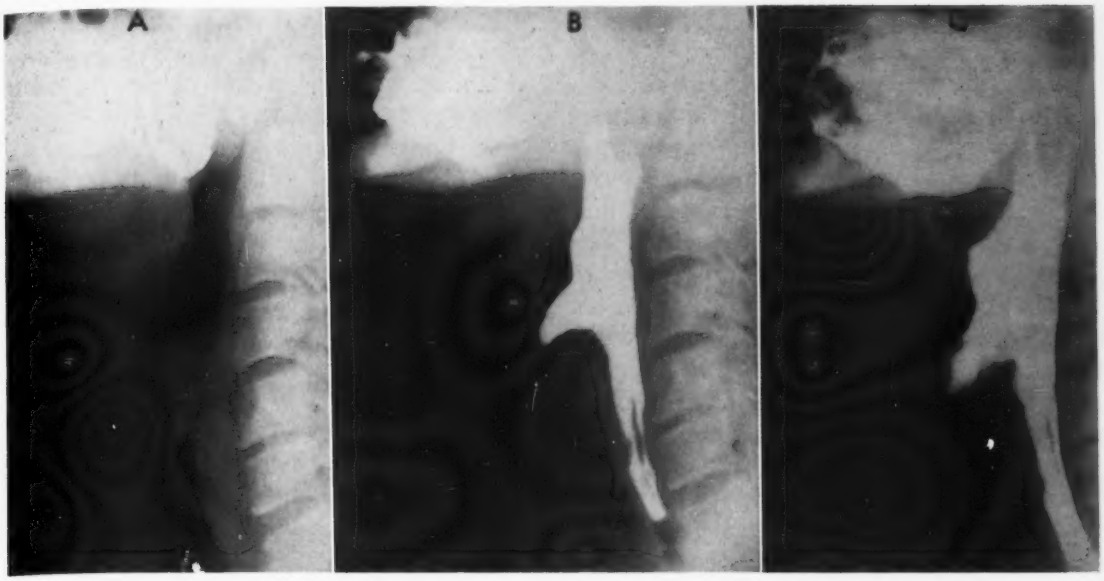

FIG. 8. Postoperative barium swallow studies. (*A*) A plain roentgenogram showing that the epiglottis is absent. (*B* and *C*) Studies showing the stages in swallowing. The barium has entered the vestibule but the cords remain closed, protecting the trachea.

and the patients might be better treated by adequate irradiation. With improved methods of selection of patients and better defined treatment factors, conservation of function falls within the scope of radiation therapy.

Clinical estimation of the extent of cancer involving the infraglottic and transglottic groups has been frequently in error. This is because the fixation of the cord masks the size of the tumor. Size and extent of subglottic involvement are difficult to appraise even with a mobile or partially paretic cord. In the transglottic group, tumors that involve and fix the false and true cords frequently obscure a large infraglottic extension. In addition, the base of the epiglottis is sometimes overlooked. In all of these situations, laryngograms have proved their value by precisely localizing and sharply delineating the lower extent of the tumor. At this institution, radiation therapy is considered the method of choice for patients with glottic cancer and mobile cords, with a resultant five year cure rate approaching 90 per cent. Involvement of the false cord and infraglottic space increases the incidence of lymph node metastases and these factors plus fixation of the cord alter the prognosis. It is felt that radiation therapy should be considered in cases of glottic lesions with a fixed cord or with infraglottic extension; however, the present trend of treatment for these lesions has been surgical. Laminagraphy, in our experience, has correlated poorly with the findings at surgery. By laryngography a baseline for future follow-up examinations can be established from which the response of the tumor to irradiation can be ascertained.

SUMMARY AND CONCLUSIONS

1. Laryngography, while not a screening procedure, has proved to be an accurate diagnostic technique in lesions of the larynx and pharynx.

2. Laryngography is a physiologic examination capable of recording variations objectively.

3. The entire anatomy of the larynx and hypopharynx can be recorded simultaneously.

4. It is a safe, simple, direct, rapid and accurate procedure.

5. By laryngography the size and location of the lesion can be determined more accurately than by clinical evaluation.

6. An analysis of data obtained from a study of total or subtotal laryngectomies with routine *en bloc* neck dissection has given us very valuable information as to certain characteristics of the primary lesion.

7. The size of the tumor, degree of differentiation and the location have a relationship to clinically apparent and inapparent cervical metastatic spread.

8. An accurate clinical classification of cancer of the larynx is necessary since the choice of therapy is governed by the probability or location of metastases.

9. A pathologic classification based on the location of the primary lesion is suggested for laryngoscopic and clinical use. Since the proposed classification indicates that there is a progressive increase in metastatic rate from glottic to infraglottic, to supraglottic, to transglottic cancers, the type of treatment to be administered can be determined.

10. The indications will be based on: (a) conservation of function by radiation therapy for early lesions of the cord; (b) larynx-sparing therapy for selected cases of supraglottic or pyriform sinus lesions; or (c) more radical operations (total laryngectomy to include neck dissection) when the inapparent metastatic rate is high.

11. Laryngograms can demonstrate graphically the response of lesions to irradiation and is an accurate documentary method of following patients after therapy.

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Vol. 86, No. 4

LARYNGEAL PATHOLOGY ON THE CONVENTIONAL ROENTGENOGRAM OF THE CHEST*

DIAGNOSTIC AND PROGNOSTIC SIGNIFICANCE

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IN THE interpretation of routine chest roentgenograms, careful scrutiny of the air column overlying the cervical spine can prove to be a truly rewarding effort. The radiologist may be the first to recognize early carcinoma of the laryngopharynx or trachea as well as vocal cord paralysis secondary to recurrent laryngeal nerve involvement.

Earlier detection of carcinomas of the laryngopharynx, prior to the appearance of gross clinical symptomatology, can provide a greater probability for cure by surgery and/or radiation. The radiologist's early roentgenographic report of laryngeal nerve paralysis is the basis for further investigative studies to determine the etiologic factor. Attention is thus promptly directed to primary or secondary malignant disease in the neck, thorax or elsewhere. In such instances, the roentgen findings may become of paramount importance in planning appropriate clinical management of the patient.

In a study of paralyzed vocal cords which we recently completed,[12] it became apparent that the roentgen evidence was frequently overlooked by the radiologist during roentgenographic and fluoroscopic examinations not specifically related to the larynx—such as studies of the cervical spine and ribs, esophagus and chest, both conventional and laminagraphic. In many of these instances, the attending physician was entirely unaware of the laryngeal pathology. In our department today, patients are promptly summoned for indirect mirror examination of the larynx as soon as abnormalities of the cervical air column are recognized on routine roentgenologic examinations.

In the interpretation of the visualized larynx on routine roentgen study, the radiologist must first determine whether the exposure was made during inspiration or expiration. The roentgen appearance of the larynx or glottis differs greatly in these two phases. In our recent communication,[12] we have described in detail these findings during laminagraphic examination of the vocal cords. It is striking how well these can be visualized on the conventional chest roentgenogram.

In inspiration (Fig. 1, *a* and *b*) the glottic aperture is wide, with no visualization of the ventricles; in expiration, the glottis is reduced to a narrow slit, as in phonation, and the ventricles are filled with air (Fig. 1, *c* and *d*). Usually, when the roentgenographic exposure is to be made, the subject is told to take a deep breath and hold it; or to take a breath, let it out and then hold it. If the exposure is made during any part of inspiration, the roentgenogram will show a wide glottis (Fig. 1, *a* and *b*). If the patient is at the termination of the inspiratory phase or at the beginning of expiration, he will suddenly stop his breathing and, in addition, may bear down slightly, thereby carrying out a modified Valsalva maneuver and the roentgenogram will show the vestibule, ventricles, glottis and trachea (Fig. 1, *c* and *d*).

Among the following illustrative cases there are 2 patients with carcinoma of the right vocal cord and 3 patients with paralyzed vocal cords due to recurrent laryngeal nerve involvement by metastatic mediastinal disease.

REPORT OF CASES

CASE 1. A sixty-seven year old white male

* From the Radiology Service of the Veterans Administration Hospital, 130 West Kingsbridge Road, Bronx, New York.

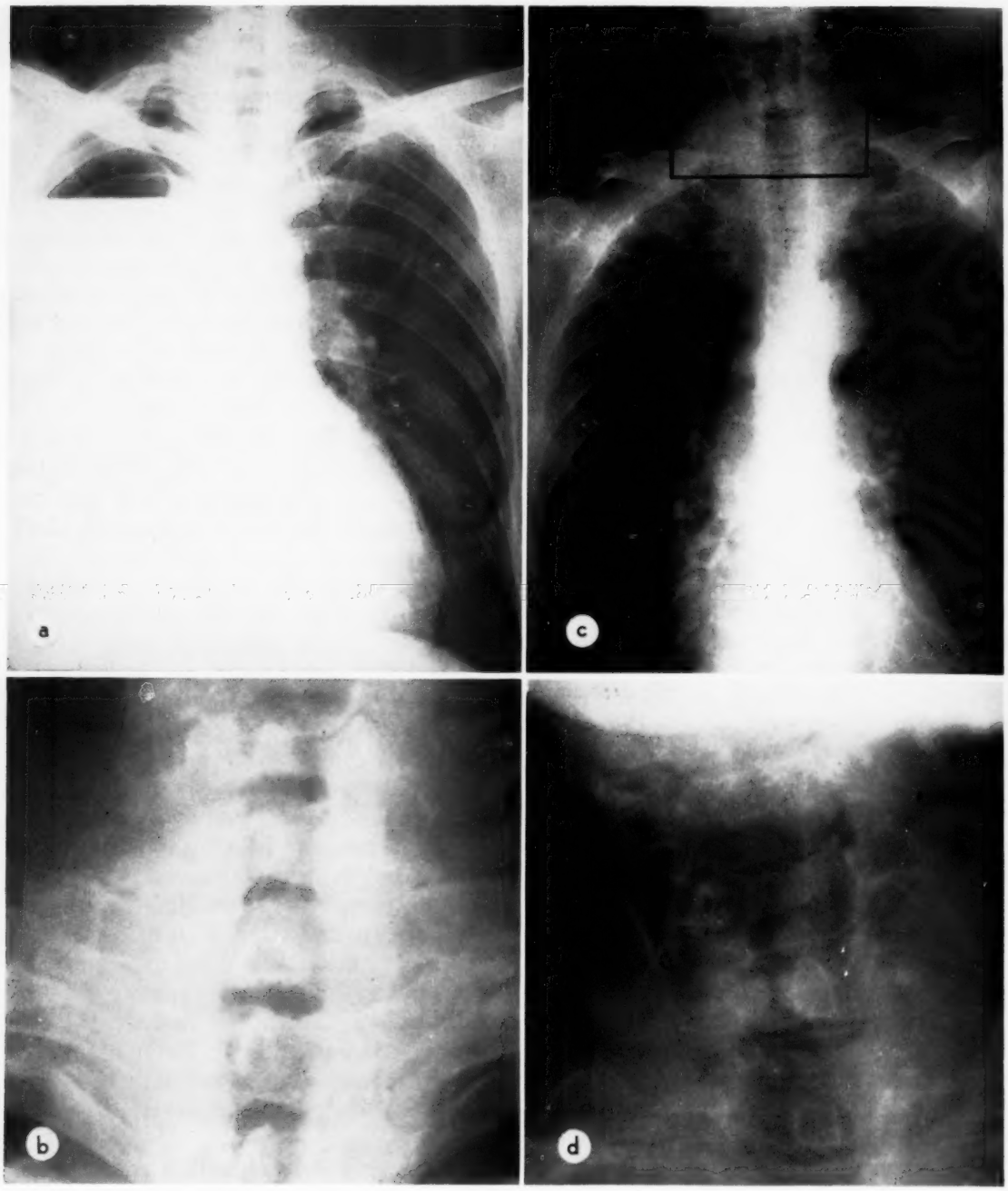

Fig. 1. (*a* and *b*) In inspiration. (*c* and *d*) In expiration. Normal anatomy of the laryngopharynx during the respiratory phases.

was admitted because of hoarseness. The admission chest roentgenogram (Fig. 2*a*) showed marked asymmetry of the glottis and a fixed right vocal cord was suspected. The air column is shown in Figure 2*b* in the marked zone. The roentgenogram was taken in inspiration and the fixed right vocal cord is very apparent. Direct laryngoscopy showed a fixed right vocal cord which was completely covered with an exophytic granular mass which involved the right ventricle and extended to the anterior commissure and the left vocal cord as well. The total laryngectomy specimen (Fig. 2*c*) shows the entire vocal cord to be replaced by epidermoid

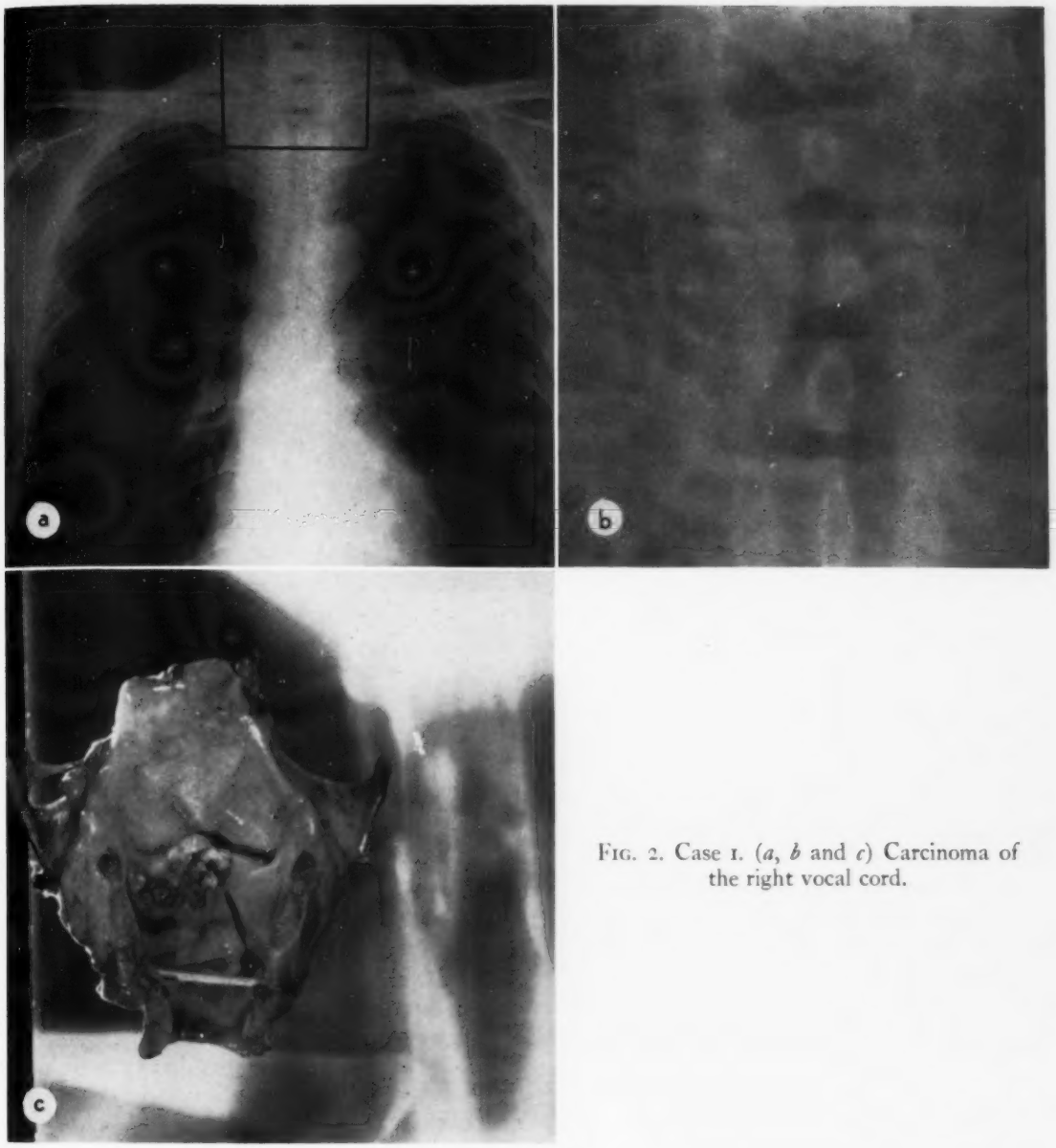

Fig. 2. Case 1. (*a*, *b* and *c*) Carcinoma of the right vocal cord.

carcinoma which has extended beyond the anterior commissure to the left vocal cord. Adjacent to the specimen is a laminagram made during phonation showing poor filling of the right pyriform sinus, asymmetry of the lower part of the vestibule, incompletely filled and slightly elevated right ventricle, fixation of the right vocal cord, slightly widened glottis, and irregular left vocal cord. These roentgen findings are diagnostic of a carcinoma of the right vocal cord.

Case II. A seventy-two year old male was admitted because of pain on swallowing and hoarseness. Figure 3*a*, which is part of an esophagram, reveals obvious asymmetry of the glottis and a fixed right vocal cord. Figure 3*b*, a magnification of the marked zone shown in 3*a* during inspiration, demonstrates marked irregularity of the right vocal cord. Figure 3*c*, a laminagram taken during phonation, shows no aeration of the pyriform sinuses. The vestibule is irregular in its inferior portion and poorly filled; the ventricles are small and poorly outlined; the glottis is small and displaced to the left; the right vocal cord is irregular, but the left vocal cord is normal. These roentgen find-

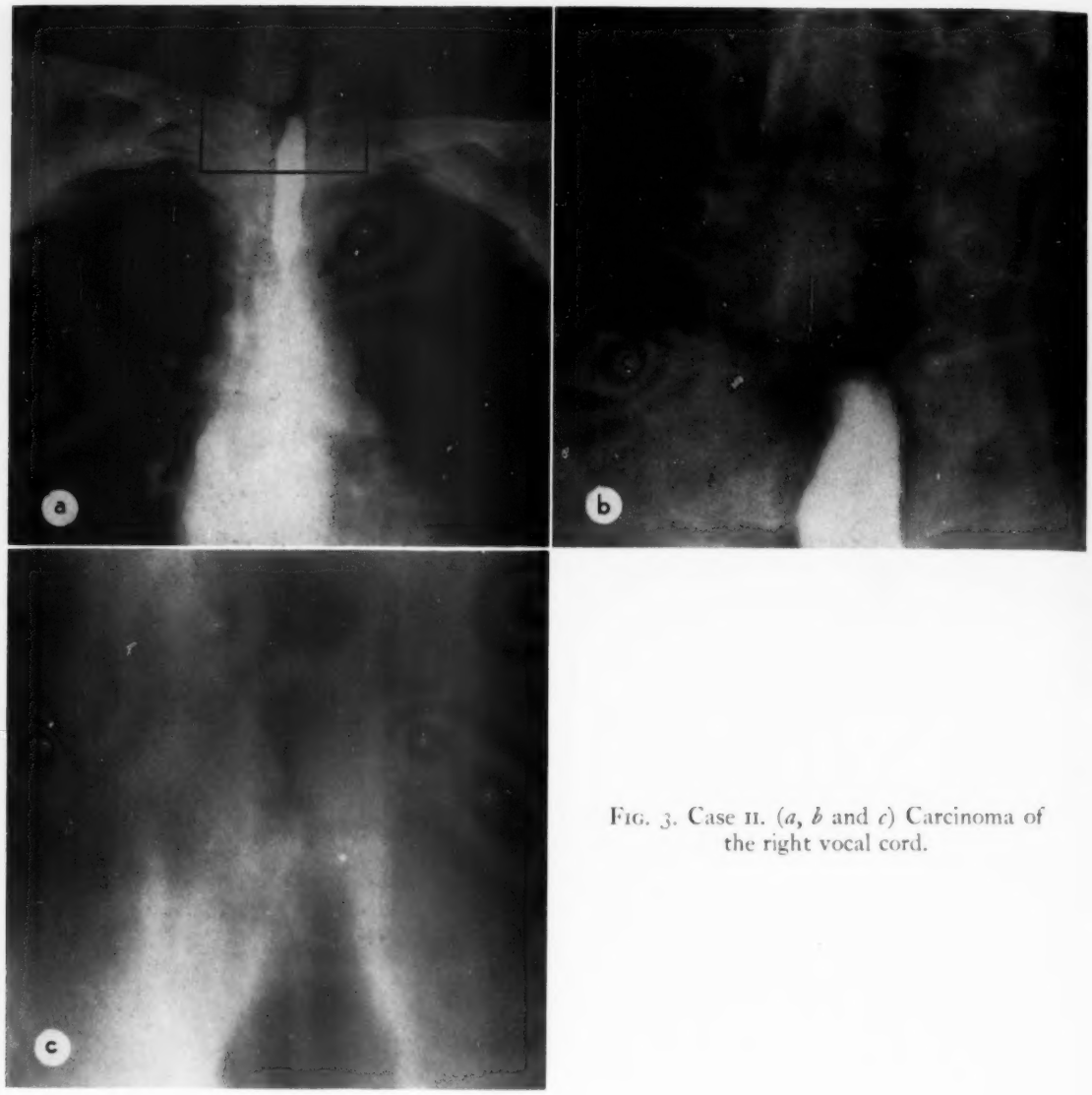

Fig. 3. Case II. (*a*, *b* and *c*) Carcinoma of the right vocal cord.

ings indicate a carcinoma of the right vocal cord. Direct laryngoscopy showed an epidermoid carcinoma in the right tonsillar region extending inferiorly along the right lateral and posterior pharyngeal wall to the right pyriform sinus and cricopharyngeus muscle. The right vocal cord was completely involved with tumor and was fixed at the midline.

Case III. A sixty-two year old male was admitted because of dysphagia. Figure 4*a* was taken shortly after barium studies of the esophagus were carried out. There is retained contrast material within a dilated upper third of the esophagus. The narrowed segment of a constricting neoplasm in the esophagus is seen above the aortic arch. The air column of the larynx is that seen in quiet respiration and shows marked asymmetry, indicating a hypertrophied right vocal cord and paralyzed left vocal cord. Figure 4*b*, a laminagram in phonation, shows incomplete aeration of the lower part of the left pyriform sinus, asymmetry of the lower part of the vestibule, a dilated left ventricle, a normal right ventricle, a glottis displaced slightly to the left and a hypertrophied right vocal cord. These roentgen findings are diagnostic of a paralyzed left vocal cord secondary to recurrent laryngeal nerve involvement. Esophagoscopy showed, in addition to an

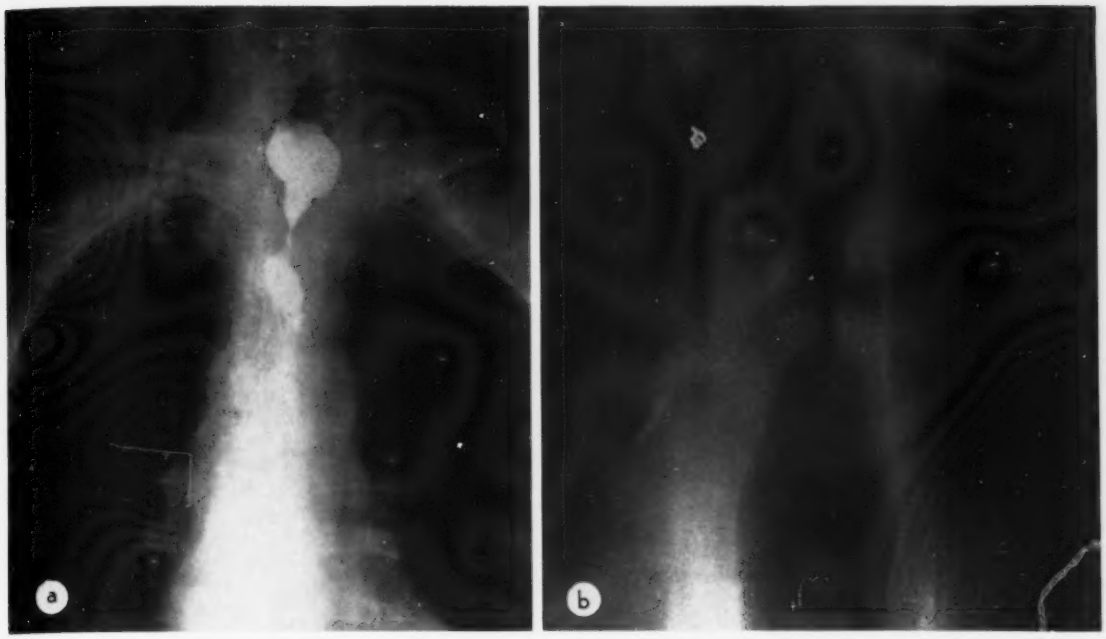

Fig. 4. Case III. (*a* and *b*) Paralysis of the left vocal cord secondary to recurrent laryngeal nerve involvement by esophageal carcinoma.

epidermoid carcinoma of the esophagus, a paralyzed left vocal cord.

Case IV. A fifty-eight year old male was admitted with an unresectable bronchogenic carcinoma of the left upper lobe, proved by thoracotomy. Figure 5*a* was to have been a Bucky chest roentgenogram, but it also included the cervical spine. In addition to the left upper lobe neoplasm, the irregularity of the larynx is very distinct. Figure 5*b*, an enlargement of the marked zone in 5*a*, shows the glottis in inspiration, characterized by a paralyzed left vocal cord fixed in adduction. This was reported as such. Figure 5*c*, a laminagram in phonation, shows the pyriform sinuses and the vestibule to be poorly aerated, the left ventricle elevated and slightly larger than the right ventricle, the glottis displaced slightly to the left, and the right vocal cord hypertrophied. These findings indicate paralysis of the left vocal cord secondary to recurrent laryngeal nerve involvement.

Case V. A seventy-two year old male had an unresectable bronchogenic carcinoma of the right middle lobe. A Bucky chest roentgenogram (Fig. 6*a*), made because of rib metastases, shows asymmetry of the glottis. An enlargement of the marked zone in 6*a* (Fig. 6*b*) shows the appearance of the glottis in inspiration, with a paralyzed left vocal cord fixed in adduction. Figure 6*c*, a laminagram in inspiration, shows air in the pyriform sinuses and vestibule, a normal right vocal cord, and a fixed and paralyzed left vocal cord. The left ventricle is filled with air and the right ventricle is partially obliterated by the mobile normal right vocal cord.

Figure 6*d* is a laminagram in phonation. Even though there is motion, the findings are characteristic of left vocal cord paralysis. Both pyriform sinuses are poorly filled with air, while the vestibule is well aerated and asymmetric in its lower portion. Both ventricles show irregular margins, but the left ventricle is larger than the right ventricle. The glottis is displaced towards the left, and the right vocal cord is hypertrophied. The roentgen findings indicate paralysis of the left vocal cord secondary to recurrent laryngeal nerve involvement.

SUMMARY

The diagnostic value of scrutiny of the air column overlying the cervical spine on routine roentgenograms of the neck and thorax is briefly discussed. The prognostic value of this observation by the radiologist

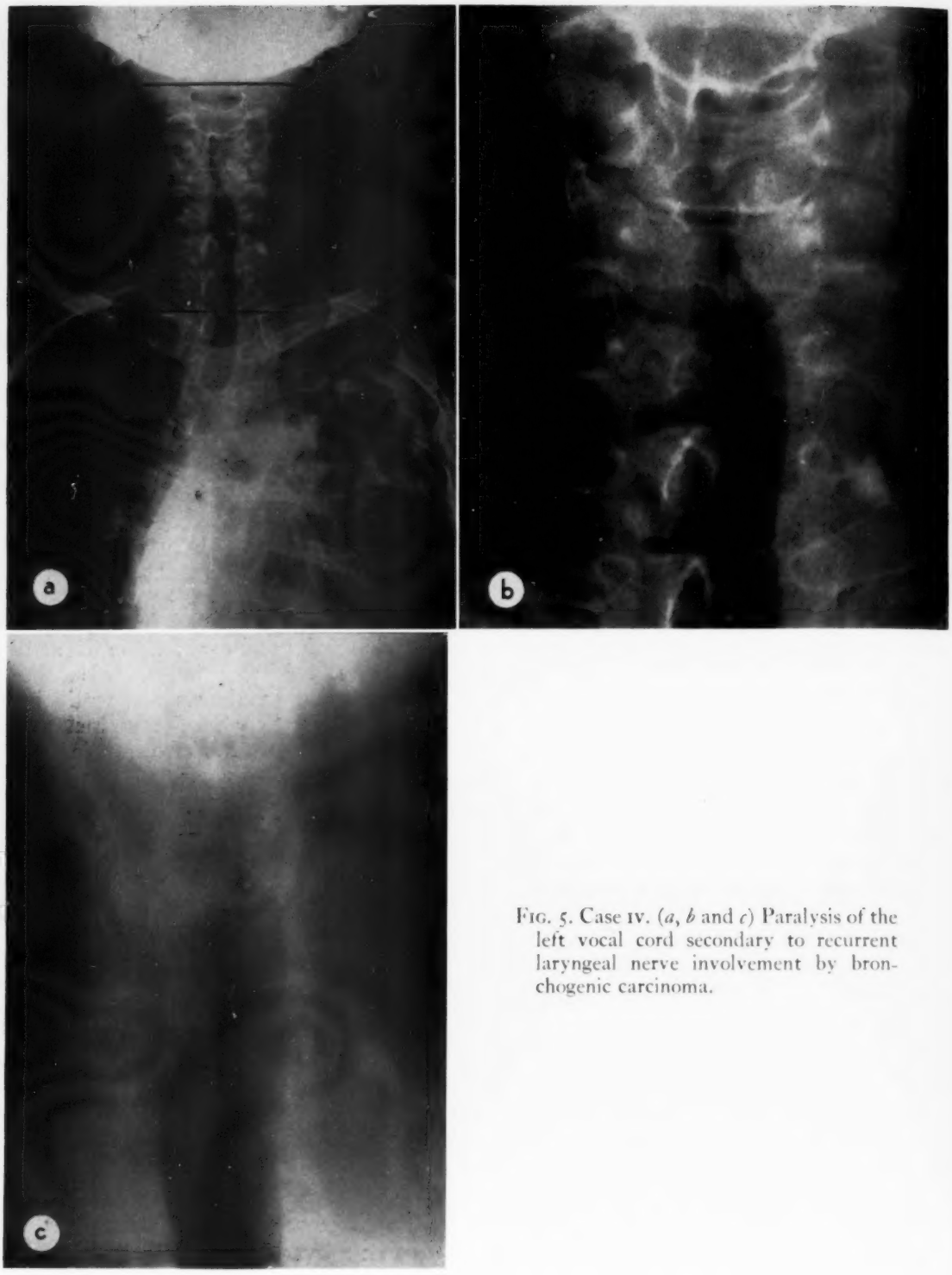

Fig. 5. Case IV. (*a*, *b* and *c*) Paralysis of the left vocal cord secondary to recurrent laryngeal nerve involvement by bronchogenic carcinoma.

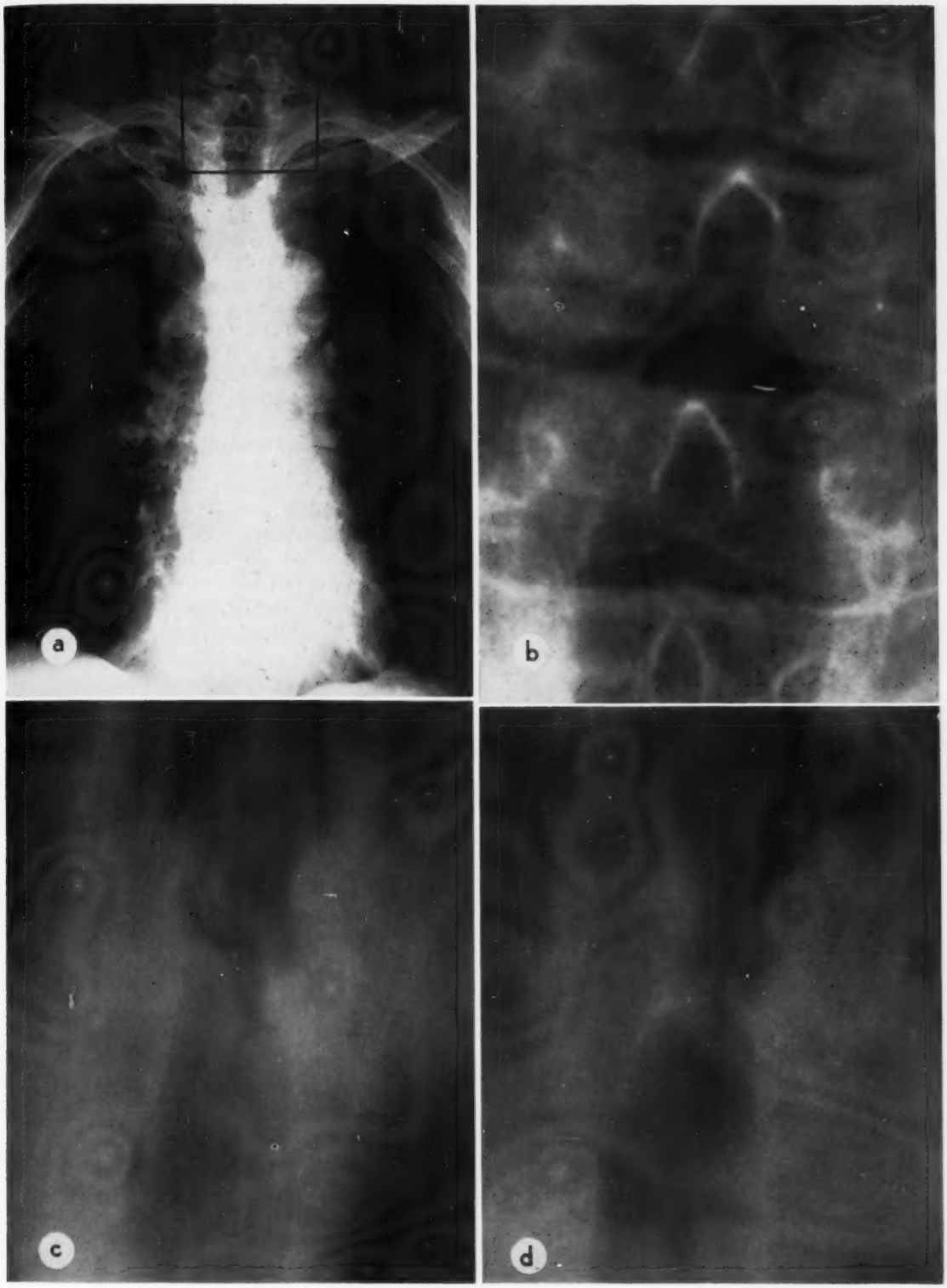

Fig. 6. Case v. (*a*, *b*, *c* and *d*) Paralysis of the left vocal cord secondary to recurrent laryngeal nerve involvement by bronchogenic carcinoma.

needs greater emphasis. Illustrative cases of abnormalities in the air column due to carcinoma of the larynx or paralysis of a vocal cord secondary to recurrent laryngeal nerve paralysis are presented.

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PRIMARY SEMINOMA OF THE MEDIASTINUM*

REPORT OF A CASE WITH AN UNUSUAL SITE OF METASTASIS AND REVIEW OF THE LITERATURE

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THE origin of primary germinal tumors of the mediastinum is not fully understood. Whether or not these growths are actually primary mediastinal tumors has been the subject of much controversy in the literature, as have been their origin, development, and the relationship between various sex-cell tumors. We are presenting the report of a case in which this rare tumor metastasized to an unusual site. We discuss the literature with respect to the theories that have been proposed to explain the origin of these neoplasms.

REPORT OF A CASE

A thirty-five year old white man was first examined at Cleveland Clinic in August, 1957. His chief symptoms were a sensation of pressure in the chest and shortness of breath. The patient had a "cigarette cough" for many years; it became productive with small amounts of yellow sputum in April, 1957. In March, 1957, a sore throat developed. In July, substernal pain became extremely severe. The patient lost 10 pounds in weight.

Physical examination. The tonsils were slightly infected. A left supraclavicular lymph node was palpable. Breath sounds were decreased over the left hemithorax, and percussion revealed that the mediastinum was widened superiorly. There were no other positive findings. The testes were normal.

Diagnostic procedures. The laboratory findings were essentially normal. Roentgenograms of the chest made on August 1, 1957, showed evidence of a mass in the left superior mediastinum which displaced the esophagus slightly to the right (Fig. 1). A biopsy of a left supraclavicular lymph node was performed, and the pathologic diagnosis was seminoma. On microscopic examination sections revealed a neoplasm composed of atypical epithelial cells forming fairly uniform islands, separated from one another by slender tracts of fibrous stroma. The cells were polygonal with clear cytoplasm, and vesicular nuclei with prominent nucleoli. Scanty plasma-lymphocytic infiltration was seen throughout the sections.

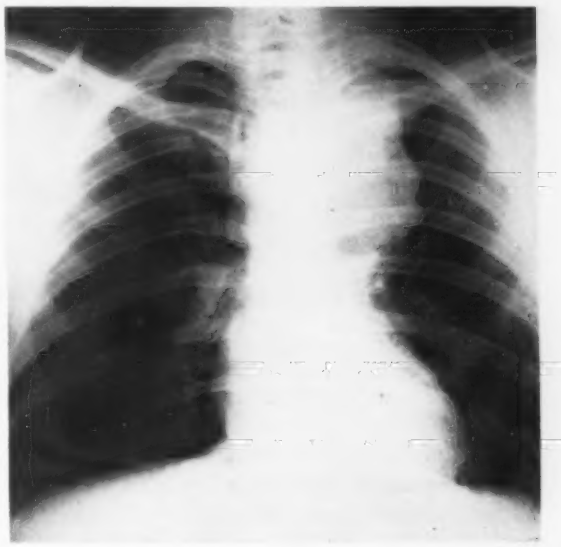

FIG. 1. Chest roentgenogram, August 1, 1957, showing a mass in the left superior mediastinum.

Course of the disease. The patient received a tumor dose of 3,000 r to the superior mediastinum with cobalt 60 teletherapy in a period of two weeks. A roentgenogram of the chest made on September 17, 1957, showed the mediastinal mass to have markedly decreased in size (Fig. 2). The testes were re-examined and again were found to be normal. In January, 1958, the patient was asymptomatic and in excellent general condition, but in June, 1958, he experienced tightness and soreness in the throat, mainly on the right side. There was reappearance of a nonproductive cough. Ex-

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FIG. 2. Chest roentgenogram, September 17, 1957, showing marked regression of the mediastinal mass, following Co^{60} teletherapy.

amination in the therapeutic section of the Department of Radiology revealed an enlarged, ulcerated right tonsil. A biopsy was performed by a member of the Department of Otolaryngology. The pathologist's report was undifferentiated carcinoma (compatible with seminoma).

The enlargement and ulceration of the right tonsillar region regressed entirely after a tumor dose of 3,000 r with cobalt 60 teletherapy given over a period of two weeks. At the end of August, 1958, a roentgenogram of the chest showed evidence of an infiltrate in the left upper lobe, as well as increased density to the right side of the aortic arch and in the right middle lobe. The patient received another course of cobalt 60 teletherapy to the right hilus and mediastinum. A tumor dose of 3,180 r was given over a period of two weeks.

On December 19, 1958, the patient was readmitted in acute distress, with severe weakness, chest and shoulder pains, and marked shortness of breath. A tumor nodule, 2 cm. by 2 cm. in size, was present in the right tonsillar area. A roentgenogram of the chest on December 29, 1958, showed evidence of progressive and marked widening of the mediastinum with large tumor masses extending both to the right and to the left (Fig. 3). In the right hemithorax there was a large pleural effusion, apparently associated with pericardial effusion. The patient died on January 1, 1959.

Necropsy findings. A necropsy (excluding the head) revealed that the testes were normal except for greatly reduced spermatogenesis. The main pathologic diagnosis was seminoma of the anterior mediastinum. Secondary neoplasm was evidenced in the lungs, hilar lymph nodes and spleen and adrenals.

REVIEW OF THE LITERATURE

It long has been known that primary teratomata of the mediastinum do occur. Ritchie,[12] as early as 1903, reported a mediastinal growth that was, ". . . histologically identical in nature with the chorionepitheliomata." Lambert and Knox,[10] in 1920, reviewed a large number of cases and reported 2 additional cases of intrathoracic chorionepithelioma. A primary chorionepithelioma of the mediastinum was observed by Krassnianskaya[9] in 1929, and primary mediastinal teratomata with chorionepitheliomatous elements were described by Arendt[1] in 1931 and by Kantrowitz[8] in 1934. Seminoma, the most common testicular tumor, has also been encountered as a primary mediastinal tumor. Wollner, Jamplis, and Kirklin,[15] in 1955, reported 3 cases of seminoma in the mediastinum. Friedman,[5] in 1951, added 3 cases of mediastinal tumors showing the histo-

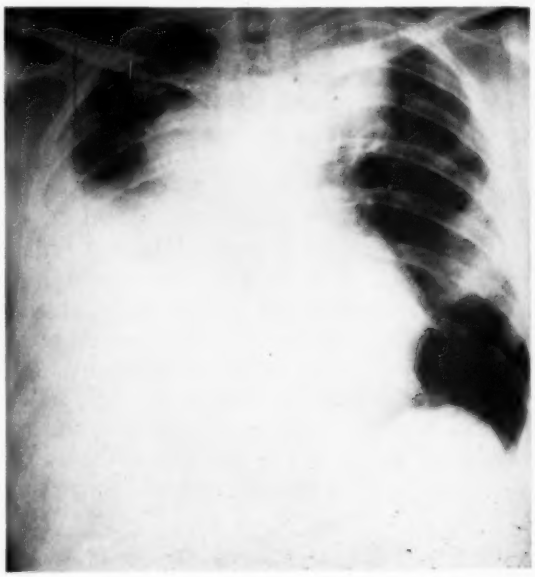

FIG. 3. Final chest roentgenogram, December 29, 1958, demonstrating bilateral mediastinal masses with pleural and pericardial effusions.

logic characteristics of germinoma. Pugsley and Carleton,[11] in 1953, found a seminomatous nodule in a primary teratocarcinoma of the mediastinum.

CLASSIFICATION

The intrathoracic germinal tumors may be classified according to cell type, as follows:

Pure: (1) teratoma, (2) chorionepithelioma, (3) seminoma.

Mixed: (1) teratoma plus chorionepithelioma, (2) teratoma plus seminoma.

THEORIES OF DEVELOPMENT

The development of germinal tumors in extragonadal sites, such as the mediastinum, the pineal gland region, the retroperitoneum, and the coccygeal area, has been the subject of interesting discussion. Most authorities believe that these tumors develop in the embryo and are present at birth. It is also rather well accepted that they are due to dissociation of tissues. According to some authors, extragonadal teratomata represent "embryonal rests," composed of entodermal and ectodermal tissues separated in the closure of the thorax.

The most practical theory, advanced by Fox and Hospers,[4] is that the primary germinal tumors of the mediastinum are due to *dissociation of totipotential cells* in the blastomere stage *before* the development of separate germ layers. These totipotential cells are thought to remain quiescent in the embryo until some future stimulus incites the cells to activity.

Another theory proposes that these tumors arise from *totipotent sex cells*. Among its advocates are Dixon and Moore,[2] Friedman and Moore,[5,6] and Scully and Parham,[13] who believe that germinoma, teratocarcinoma, chorionepithelioma, and teratoma in the pineal gland and in the region of the thymus are of germinal origin, arising from sex cells or their predecessors. How do those sex cells reach the mediastinum? Dixon and Moore[2] believe that some germ cells are left behind during the migration from the yolk sac to the gonad in early embryonic life. According to Lambert and Knox,[10] the finding of sex cells in sites outside of the gonads in some fish embryos was reported by Beard in 1902.

METASTASIS

A considerable number of the teratomata shows evidence of malignancy. It is well known that these malignant lesions may metastasize to the mediastinal lymph nodes, lungs, and sometimes to more distant sites. Only certain elements of the teratoma may take on a malignant character. Considering the developmental relationship of the germinal tumors to each other, it is not surprising that metastatic lesions of teratomata may show the histologic pattern of one of the other sex-cell tumors. According to Friedman,[5] seminomatous tissue occurs in metastatic lesions only if the primary tumor is a seminoma or if it contains seminomatous elements. Metastasis in 2 patients with chorionepithelioma of the mediastinum has been reported by Lambert and Knox.[10] Gerhartz[7] emphasized that the testicular seminoma is likely to metastasize widely to distant locations via the blood stream. Primary seminoma of the mediastinum shows a similar tendency.

With regard to the metastases of the seminoma found in our case, it is interesting that Wilson and Cares[14] reported a metastatic lesion of a mediastinal teratoma to the posterior triangle of the neck, and that Findlay[3] found malignant tissue in the mouth of a patient who had a malignant seminoma of the testis. Apparently, the mediastinal seminoma has the ability to metastasize to unusual sites.

SUMMARY

A case report of the rare primary seminoma of the anterior mediastinum with an unusual metastasis to the tonsil has been presented. The literature has been reviewed with special respect to the origin of the mediastinal seminoma.

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ACTINOMYCIN D AND ROENTGEN-RAY THERAPY IN THE TREATMENT OF METASTATIC WILMS' TUMOR*

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ACTINOMYCIN D, an antibiotic which was isolated from cultures of *Streptomyces parvallus*, has been shown to have an antineoplastic activity in tumors in children, particularly Wilms' tumor, neuroblastomas, and embryonal rhabdomyosarcomas.[2] Shaw *et al.*[3] reported definite antitumor response in 3 of 5 patients with Wilms' tumor. The method of action of actinomycin D may be by inhibiting ribonucleic acid synthesis.

The complications of actinomycin D therapy have been enumerated by Tan *et al.*[4] and consist of:

1. Redness and ulceration of the buccal mucosa beginning one to three days after an intravenous dose and lasting three to five days.

2. Vomiting four to five hours after each injection, and nausea, anorexia, occasional abdominal pain or diarrhea during therapy.

3. Erythema and occasional vesiculation and exfoliation over previously treated areas.

4. The falling out of hair and sometimes of the eyebrows in varying severity at seven to ten days after the intravenous course, with regrowth occurring after two to four weeks.

5. Leukopenia, usually temporary, occurring in the range of 2,000 white blood cells per cubic millimeter, and occasionally less than 1,000 white blood cells per cubic millimeter. This is more severe if the patient is receiving both roentgen-ray and actinomycin D therapy.

6. Platelets dropping to less than 100,000 per cubic millimeter in 30 per cent of patients.

7. Rising of the uric acid concentration in serum (14 of 93 patients in the series of Tan *et al.*[4]).

When actinomycin D and radiation therapy were given concomitantly, D'Angio *et al.*[1] noted (1) early erythema in the area of irradiation, (2) reduction in the time required for the normal progression of radiation effects, and (3) enhanced skin manifestations leading to dangerously severe local reactions following high concomitant dosages.

These effects have all been confirmed in animal experimentation.

Tan *et al.*[4] reported a favorable response in 6 of 16 patients with metastatic Wilms' tumor in whom actinomycin D therapy was used alone, and in 13 of 17 patients in whom combined roentgen-ray and actinomycin D therapy was employed.

Our discussion is limited to a brief description of a group of patients with Wilms' tumor with metastatic disease and the response of these cases to combined therapy. The dosage of actinomycin D was 75 μg. /kg. body weight divided into 5 equal daily doses unless otherwise stated.

REPORT OF CASES

CASE 1. A. V., a five year old white male child, was admitted to Variety Children's Hospital on July 10, 1957 with hematuria and a left flank mass. He was transferred to Jackson Memorial Hospital, where a left nephrectomy was performed seven days later.

He received postoperative roentgen-ray therapy consisting of 3,000 r (factors 250 kv., 50 cm. target skin distance, half value layer 2.5 mm. Cu) each to left upper quadrant anterior and posterior portals. The child reportedly did

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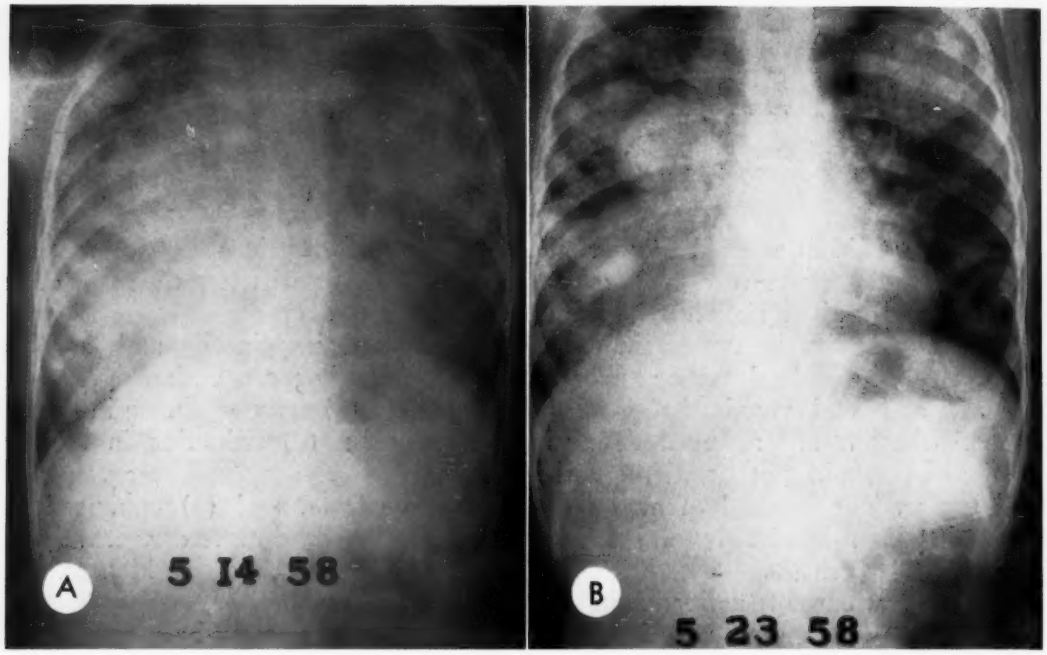

Fig. 1. Case 1. (*A*) Admission chest roentgenogram revealing far advanced metastatic disease to the lungs. (*B*) Posteroanterior chest roentgenogram five days after institution of actinomycin D therapy.

well until just prior to re-admission to Variety Children's Hospital with meningeal symptoms and marked shortness of breath ten months after the original admission. The chest roentgenogram revealed far advanced metastatic lesions in both lung fields. The child was failing rapidly, and therapy with actinomycin D was begun four days after admission (Fig. 1–4). Within eleven days marked improvement was observed. The only toxicity was vomiting, reduction in platelets from 200,000 to 21,000, and bronzing of the previous roentgen-ray portal. He was discharged from the hospital and followed in the tumor clinic.

Improvement continued for three months, at which time recurring metastases were noted in the chest. These nodules doubled in size in fourteen days, and a second course of actinomycin D was given. A five week remission was obtained. A third dose of actinomycin D was then administered, but to no avail.

Following this, roentgen-ray therapy to the chest and administration of nitrogen mustard resulted in a four week remission, and then, in an attempt to stop the progression of the lesions, mitomycin C (200 μg./kg.) was given for a period of two days. Temporary relief was afforded, but on March 2, 1959, twenty months after the original admission, the child was re-admitted and had a progressive downhill course to death. He survived ten months after what appeared to be his terminal admission and was quite comfortable and happy for about eight of these ten months.

Case II. S. L., a three year old white male child, was admitted to Variety Children's Hospital on March 17, 1958, two weeks after his mother discovered a nontender hen's egg sized mass in the left upper quadrant. Three days prior to admission the mother noted a large, swollen, not tender, bluish discoloration of the left side of the scrotum. Roentgen examination revealed a mass lesion in the superior pole of the left kidney, which displaced the kidney inferiorly, and metastases to the lungs (Fig. 5–9). At surgery all of the lymph nodes were not removed.

He received postoperative roentgen-ray therapy of 2,000 r to opposing 18×10 cm. portals, and a single concomitant course of actinomycin D. The lung lesions began to regress within two weeks and continued to regress for two months. At this time small nodular lesions were noted in the right lung, and a second course of actinomycin D, this time 90 μg./kg. in five divided

FIG. 2. Case 1. (*A*) Roentgenogram eighteen days following institution of actinomycin D. (*B*) Roentgenogram thirty-nine days after actinomycin D therapy.

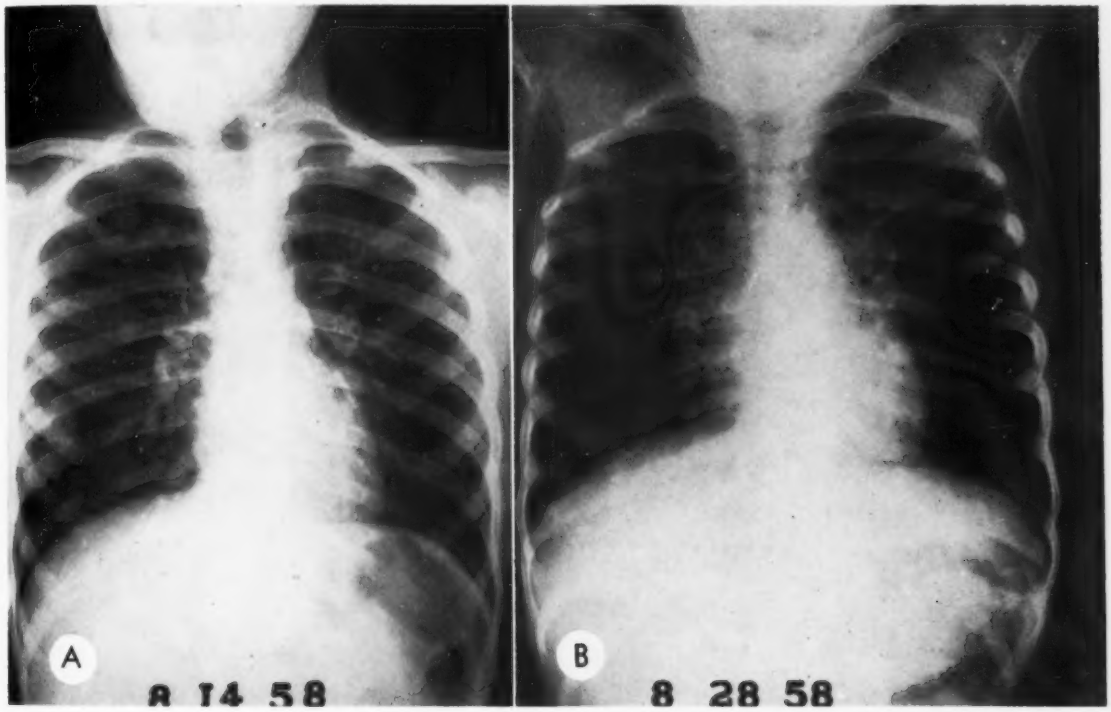

FIG. 3. Case 1. (*A*) Roentgenogram showing recurring nodule three months after institution of therapy. (*B*) Roentgenogram showing some regression two weeks after second course of actinomycin D therapy.

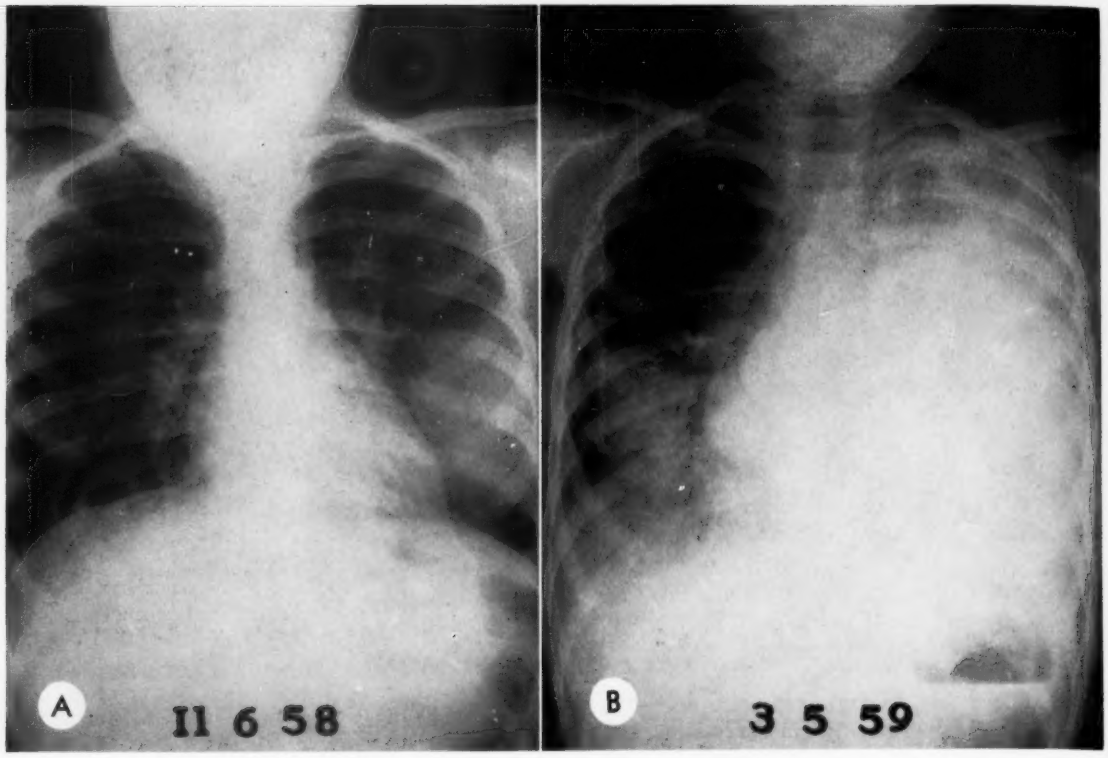

Fig. 4. Case I. (*A*) Roentgenogram showing recurrent metastatic nodules six months after start of actinomycin D therapy. (*B*) Chest roentgenogram on final admission.

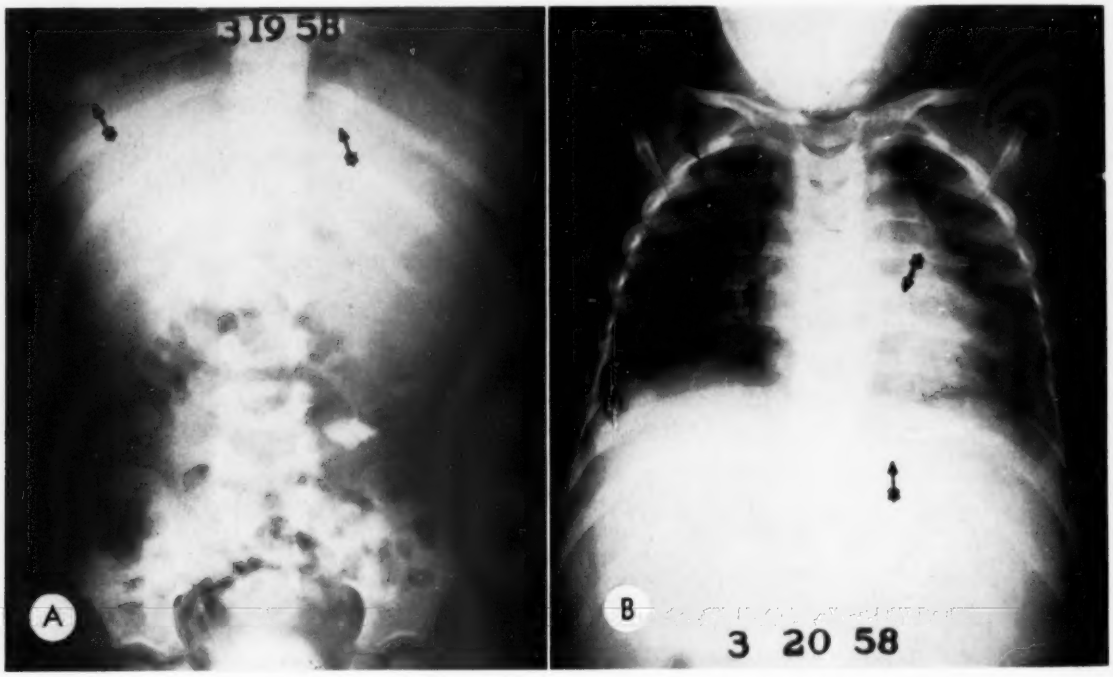

Fig. 5. Case II. (*A*) Intravenous pyelogram showing mass lesion displacing left kidney inferiorly, and two metastatic lesions in the lungs (arrows). (*B*) Admission chest roentgenogram revealing bilateral metastatic Wilms' tumor.

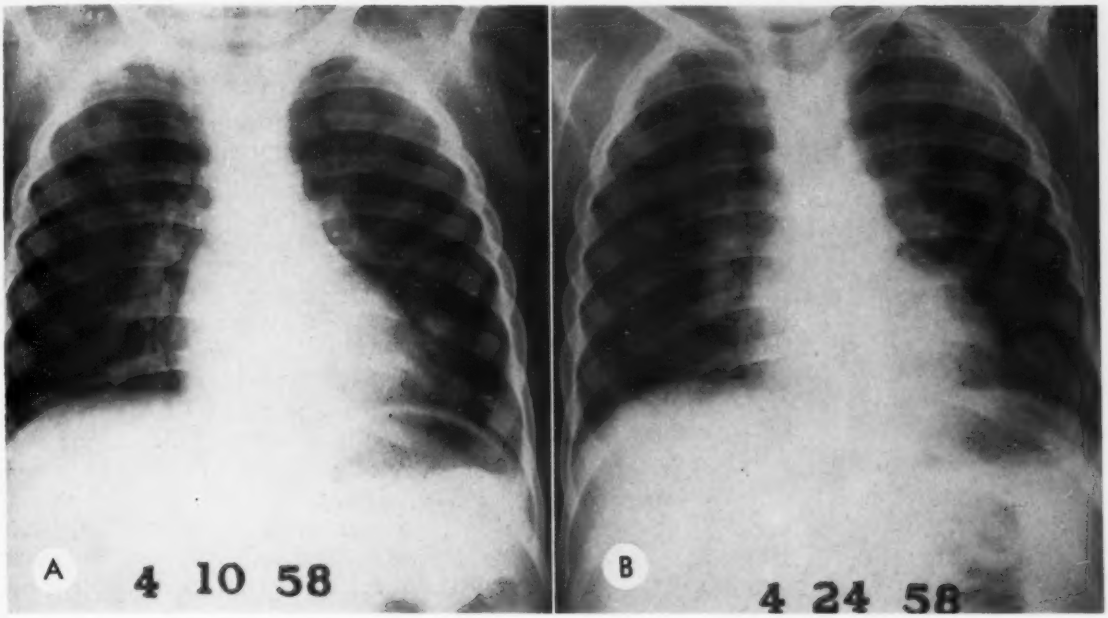

FIG. 6. Case II. (*A*) Chest roentgenogram showing metastatic lesions at beginning of combined therapy. (*B*) Roentgenogram two weeks later showing regression of metastatic lesions.

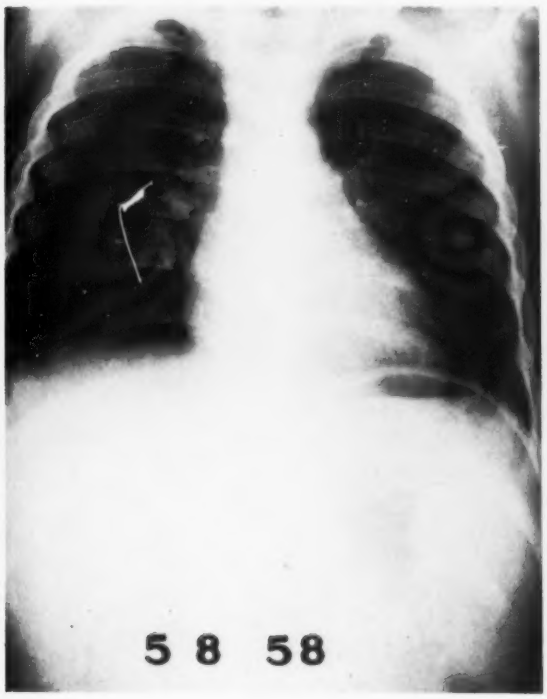

FIG. 7. Case II. Roentgenogram at completion of therapy.

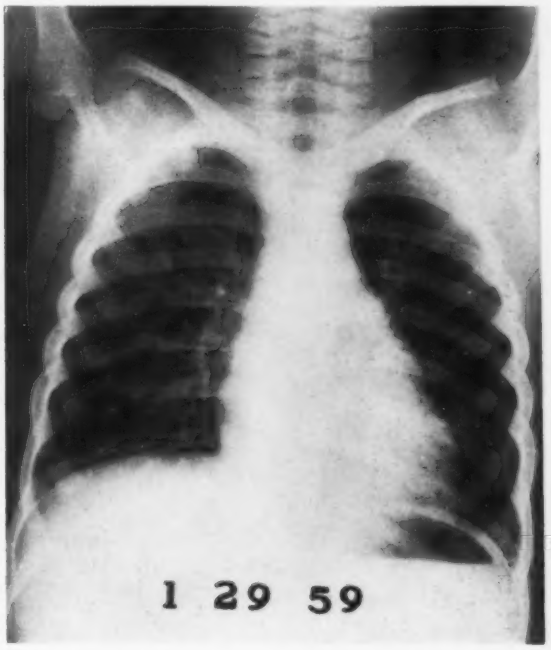

FIG. 8. Case II. Roentgenogram eight months after treatment.

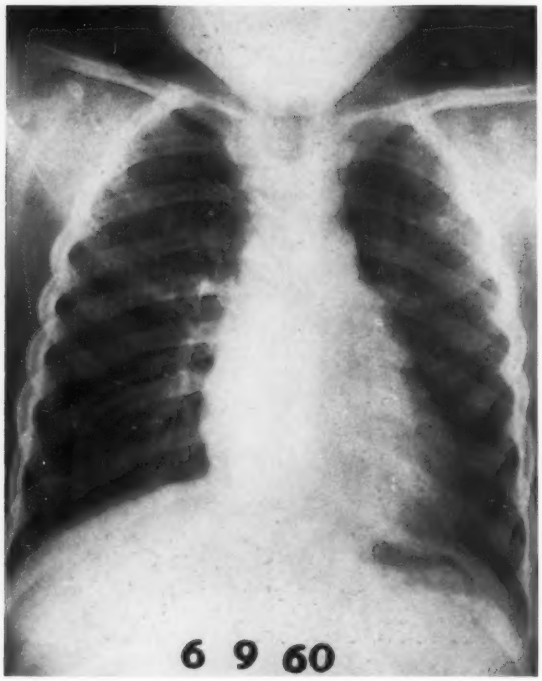

Fig. 9. Case II. Negative chest roentgenogram two years following treatment.

daily doses, was administered. Marked erythema was noted in the previously irradiated areas. The metastases disappeared within four weeks, and the child has remained well to date, three years after his initial admission.

Case III. G. V., a thirteen year old white male child, was admitted to Jackson Memorial Hospital on November 28, 1958, seven years after the removal of a retroperitoneal ganglioneuroma. At that time he was given roentgen-ray therapy through two opposing left abdominal ports, a 2,000 r air dose being administered to each port. Following this no recurrence was noted.

On this admission he complained of right lower quadrant pain. At surgery a large hemorrhagic right kidney tumor which extended into the renal vein was discovered. The pathologic diagnosis was Wilms' tumor with involvement of the renal vein. The patient received postoperative roentgen-ray therapy consisting of a 2,400 r air dose to a 10×12 cm. right anterior port and a 2,600 r air dose to a right posterior upper abdominal 10×12 cm. portal (factors 250 kv., 50 cm. target skin distance, half value layer 2.5 mm. Cu). Roentgenograms revealed no metastases to bones, skull or chest.

Two months later metastatic lesions (Fig. 10) to the chest were observed, and actinomycin D was administered. A five week remission was obtained, after which progression of metastases was again noted and a second course of actinomycin D was started. The patient's disease, however, had only a two week remission and although a third course of actinomycin D was begun, he expired.

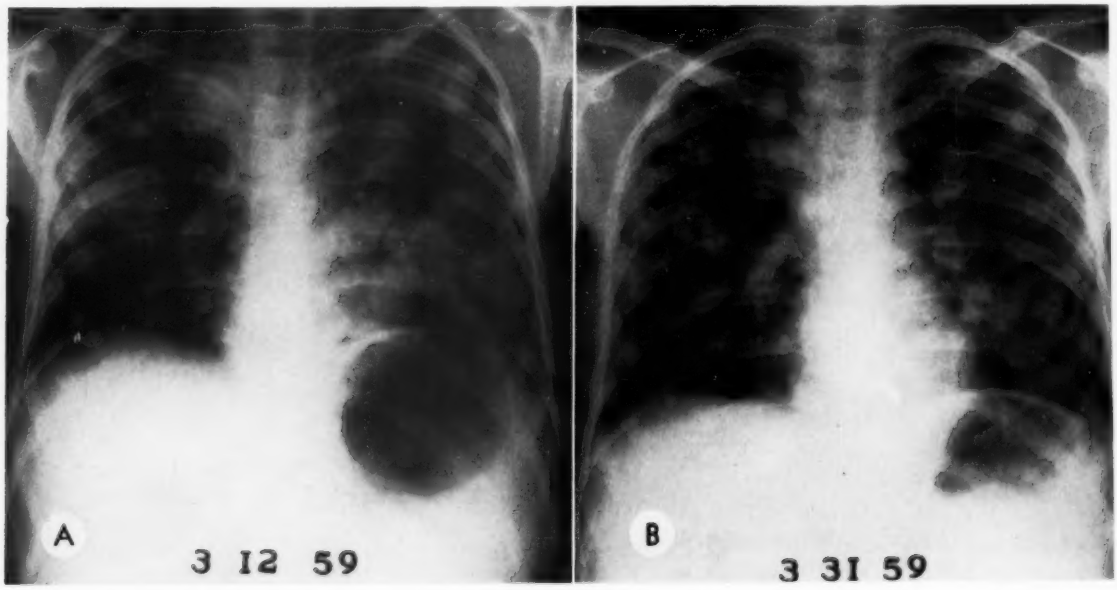

Fig. 10. Case III. (*A*) Roentgenogram showing far-advanced metastatic Wilms' tumor to the lung fields. (*B*) Roentgenogram nineteen days after institution of actinomycin D therapy.

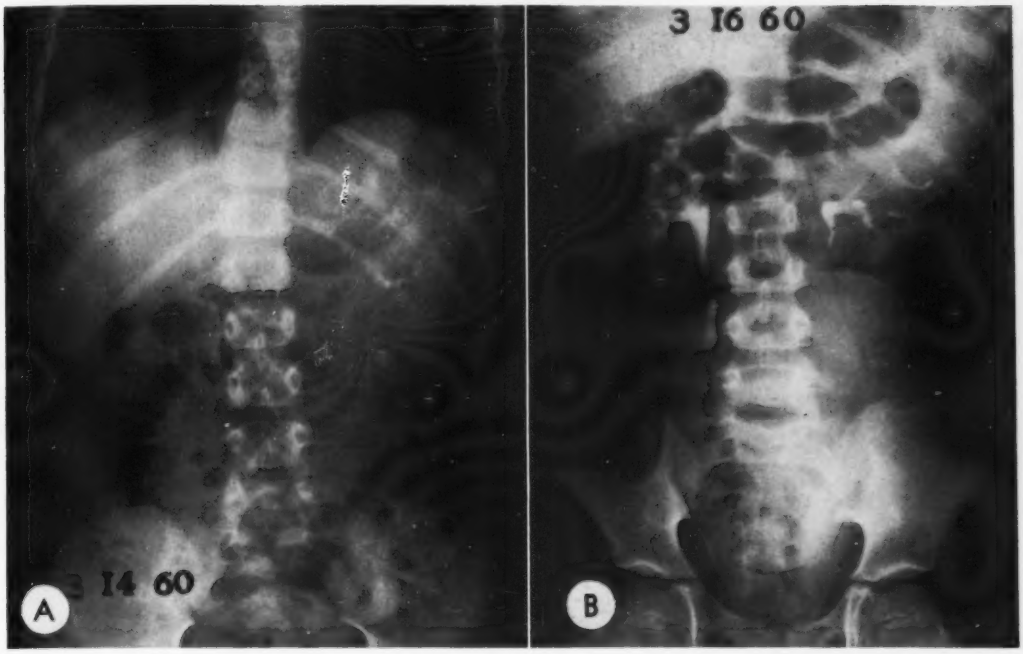

Fig. 11. Case v. (*A*) Admission abdominal roentgenogram revealing calcified mass in the left renal area. (*B*) Intravenous pyelogram revealing mass lesion (Wilms' tumor) in the upper pole of the left kidney.

Case iv. F. S., a sixteen month old Negro female child, was seen at Variety Children's Hospital on December 28, 1958 with a history of abdominal swelling of two weeks' duration. The abdomen was markedly distended with prominent veins. A large right-sided abdominal mass was palpated, the lower border of which was just above the iliac crest. Admission roentgenograms disclosed a negative chest. An intravenous pyelogram demonstrated a large mass lesion displacing the right kidney and ureter. A bone survey was negative.

Surgical exploration revealed a large Wilms' tumor of the right kidney. Silver clips were placed in the limits of the tumor bed for roentgen-ray beam direction. The pathologic diagnosis was Wilms' tumor, with metastases to the posterior and anterior lymph nodes.

Postoperative roentgen-ray therapy consisted of two 8×14 cm. opposing portals (factors 220 kv., 50 cm. target skin distance, half value layer 2.0 mm. Cu, tumor dose 4,380 r) with concomitant actinomycin D. Toxicity was noted by vomiting and diarrhea. The radiation reaction was very severe. The postirradiation roentgenogram of the chest was negative. Examination two years after surgery revealed normal growth and development without evidence of metastases.

Case v. S. P., a seven year old white female child, was admitted to Variety Children's Hospital on March 11, 1960 with a chief complaint of severe pain in the lower back and rigidity in the back and neck.

Preliminary roentgenograms of the thoracolumbar spine (Fig. 11–13), revealed a calcified mass in the left upper quadrant. An intravenous pyelogram demonstrated distortion of the upper calyceal system of the left kidney and displacement of the kidney inferiorly. A left nephrectomy was performed. The pathologic diagnosis was Wilms' tumor of the left kidney without evidence of metastases to the regional lymph nodes or renal vein.

The patient received nitrogen mustard and roentgen-ray therapy (factors 220 kv., 50 cm. target skin distance, half value layer 2.0 mm. Cu, tumor dose 4,350 r, 10×15 cm. opposing portals) which was started on the first postoperative day.

Metastases to the lung were discovered three and one-half months after admission. Actinomycin P_2 was given for five daily doses. The patient developed nausea, vomiting, and a drop in the platelet count from 190,000 to 36,000. The lung lesions showed no change for a period of one month, and then progression was seen. A course of actinomycin D was then given.

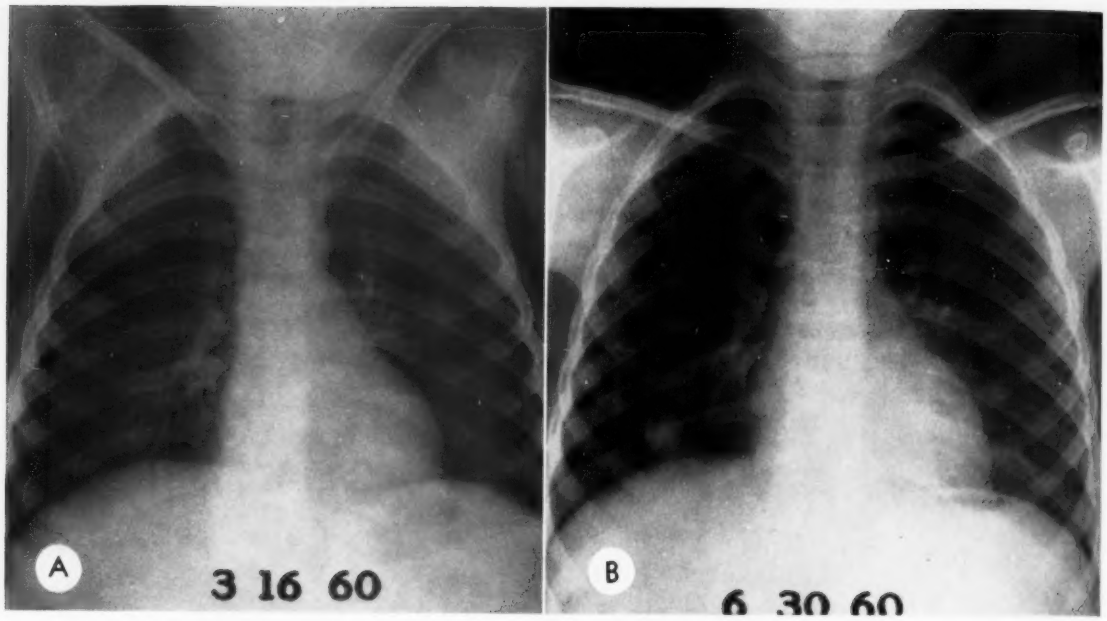

Fig. 12. Case v. (*A*) Negative chest roentgenogram on admission. (*B*) Roentgenogram showing metastatic Wilms' tumor of the right lower lobe, three months after surgery and postoperative irradiation.

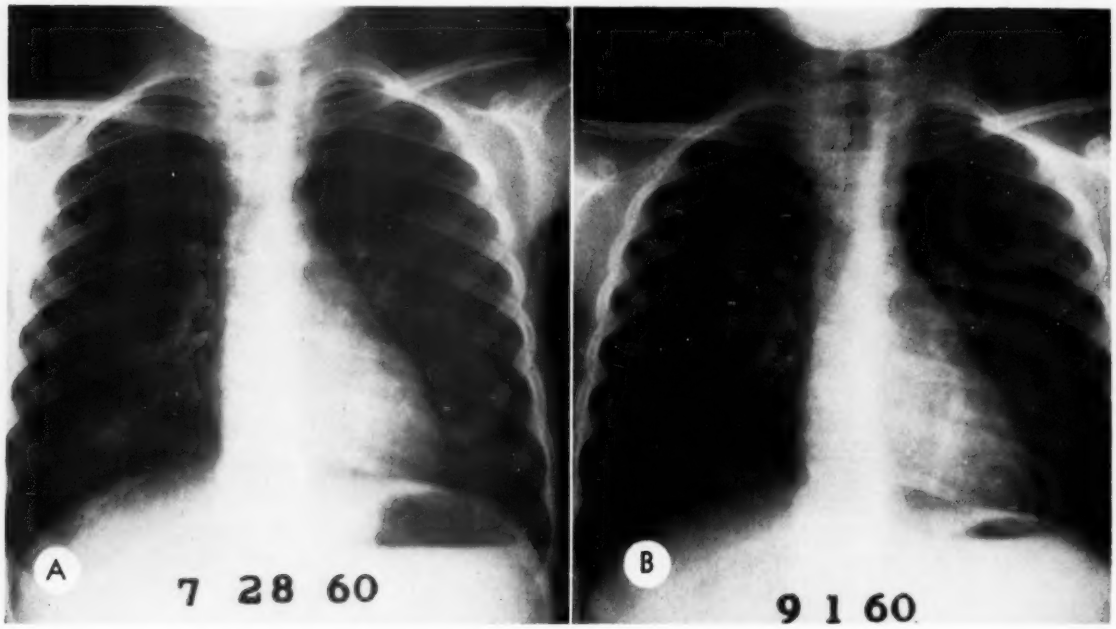

Fig. 13. Case v. (*A*) Roentgenogram showing no change of lesion one month following institution of actinomycin P_2 therapy. (*B*) Roentgenogram showing status of lesion two months following institution of therapy.

SUMMARY

Actinomycin D has a definite antineoplastic effect on metastases of Wilms' tumor. The toxic effects of the drug in the dosage used were not severe. There appears to be a potentiation of effect when actinomycin D and roentgen-ray therapy are used concomitantly. Of the 5 cases presented, the best results were obtained by the initial concomitant use of actinomycin D and roentgen-ray therapy. Two of the 5 patients in whom concomitant therapy was used initially and in whom metastases were present are well to date, 1 for three years and 1 for two. One patient in whom metastases were not found initially and who received postoperative irradiation and nitrogen mustard developed metastases within three months. This has been helped by actinomycin P_2 therapy. The other 2 patients were treated for metastatic disease primarily with actinomycin D and received moderate palliation.

CONCLUSION

Five cases of metastatic Wilms' tumor are presented, and their varying response to actinomycin D and roentgen-ray therapy is discussed.

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Kind thanks are given to James A. Whiteside, M.D., and D. G. Traggis, M.D., of the tumor clinic of Variety Children's Hospital, working under Grant #CYP 3774, National Institutes of Health, Bethesda, Maryland.

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THE ROENTGEN FINDINGS IN LYMPHOSARCOMA OF THE SMALL INTESTINE*

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THE roentgen alterations produced by lymphosarcoma of the small intestine have been considered, in general, to be too varied and nonspecific to permit a definite diagnosis. With increasing experience with small intestinal lymphosarcoma and with the recognition of the abnormal patterns produced by other small intestinal ailments, it has become apparent that primary lymphosarcoma of the small intestine often presents an appearance which is highly suggestive of the underlying pathologic alterations. It is true that lymphosarcoma of the small intestine may present in a variety of forms which, at first glance, may seem to bear little relation to each other. It will be seen, however, that the differences in the changes produced are primarily a function of the direction of growth and the multiplicity of the lesions.

Early recognition of primary neoplasms of the small intestine is difficult due to the paucity of localizing symptoms and signs relating to the disease until it is far advanced. This is particularly true of primary lymphosarcoma of the small intestine because obstruction is infrequent, in contrast to carcinomas in this region, where obstruction is often the first presenting sign. The most useful diagnostic aid is roentgen study.

A classification of the roentgen changes, therefore, is of practical usefulness. The purpose of this paper is to present the roentgen findings in a series of 75 proved cases of primary lymphosarcoma of the small intestine. They may be classified as follows: (1) multiple small nodular form; (2) infiltrating form; (3) polypoid form (intussusception); (4) endo-exoenteric form with extensive excavation, perforation and fistula formation; and (5) predominantly invasive form of the mesentery with (a) large extraluminal masses (single or multiple, with extrinsic pressure upon the small intestine), and (b) production of the sprue pattern.

GENERAL CONSIDERATIONS

The frequency of lymphosarcoma in the various portions of the small intestine roughly parallels the distribution of lymphoid tissue within the small bowel. Accordingly, it is most commonly found in the ileum where larger lymphoid collections (Peyer's patches) exist.

The tumor may arise in the lymphoid tissue of the mucosa or submucosa. It has a tendency to extend along the long axis of the bowel and may take origin from multiple sites. This is in contrast to the usual behavior of carcinomas in this region which produce a single short segmental constricting lesion.

In the initial stages, lymphosarcoma may appear as a discrete, thickened, nonulcerated plaque with relatively intact overlying mucosa. Presumably, if it arises superficially, that is, in the mucosa, growth may be predominantly towards the lumen causing no remarkable rigidity in the adjacent bowel wall. As a result, exaggerated peristalsis, occasioned by the intraluminal mass, in an attempt to expell the mass may produce an intussusception with subsequent intestinal obstruction.

Lymphosarcoma, however, may extend intramurally causing a diffuse thickening of the wall of the small intestine over a considerable distance. When this occurs in the submucosa, the folds of the mucosa may appear intact. Sometimes they may be

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smoothed out by the submucosal thickening and, on occasion, may even appear coarsely thickened. When the infiltration is more superficially located, the overlying mucosa may be thrown up into innumerable small polypoid projections. This diffusely infiltrating form is not associated with any single mass but occurs along the course of the involved bowel; alternating areas of greater and lesser involvement may be found producing a grossly irregular, rigid, unchanging appearance.

In contrast to this type of extension, that is, along the longitudinal axis of the bowel, growth may occur essentially outwards. In this situation, the mass is usually large and both endo- and exointestinal in position. As the mass grows, it destroys the intestinal wall and extends into the mesentery, infiltrating and destroying adjacent intestinal loops. Ulceration of the tumor occurs with the formation of many intercommunicating channels within the tumor mass as well as into the adjoining involved bowel loops. Ulceration and necrosis within the tumor continue producing a large irregular excavation which communicates with several loops of bowel. Perforations that occur, therefore, are rarely into the free peritoneal cavity but rather into the agglutinated mass of tumor, mesentery and small intestine.

Lymphosarcoma is a medullary tumor and as such does not evoke a desmoplastic response. As a result, there is little tendency for scirrhous tissue to form and stenosis to occur. A certain degree of narrowing of the bowel lumen may be observed due to extrinsic compression and marked thickening of the bowel wall, but stricture formation of sufficient severity to cause intestinal obstruction is rare. When it occurs, it is associated with ulceration and secondary infection. In one instance in the present series the ulceration which had evoked mechanical intestinal obstruction by producing marked spasm was not located in the tumor itself but immediately adjacent to it (Fig. 9*B*). This situation is extremely rare. Intestinal obstruction in lymphosarcoma is most often incident to intussusception.

In some cases, the infiltrated bowel wall reveals a remarkable local segmental dilatation, sometimes of "aneurysmal" character. The apparent atonicity has been explained as the result of destruction of the muscular coat by the tumor as well as involvement of the nerve plexuses.

Diffuse involvement of the mesentery by extraluminal extension of lymphosarcoma may produce alterations in absorption of nutrients from the intestinal tract. Fats, being the most difficult substances to absorb, are generally the first to be affected and steatorrhea may result. The clinical and laboratory findings may then be indistinguishable from those seen in idiopathic sprue. However, failure to respond to the usual therapy for idiopathic sprue or the subsequent development of other evidence of lymphosarcoma leads eventually to the correct diagnosis.

ROENTGEN FINDINGS

1. *Multiple small nodular defects* (Fig. 1, *A* and *B*). These appear roentgenographically as multiple pea-sized intraluminal nodules which alter the mucosal pattern of the bowel and produce an irregular, coarse scalloping of the bowel contour. The bowel lumen may be of normal or increased caliber. It is not narrowed. These changes are usually found in the ileum and involve segments varying from one to two feet in length. The involved segment retains its pliability and is not fixed in position.

This form may occur as the sole manifestation of the disease or may be associated with other small intestinal changes. We have observed 5 such cases. In 3, the colon was also involved. The colonic changes are similarly nodular and may simulate the roentgen alterations seen in familial polyposis. The changes in the colon may not be seen as easily as those in the small intestine because the lumen of the colon is large and distensible and the tiny nodular

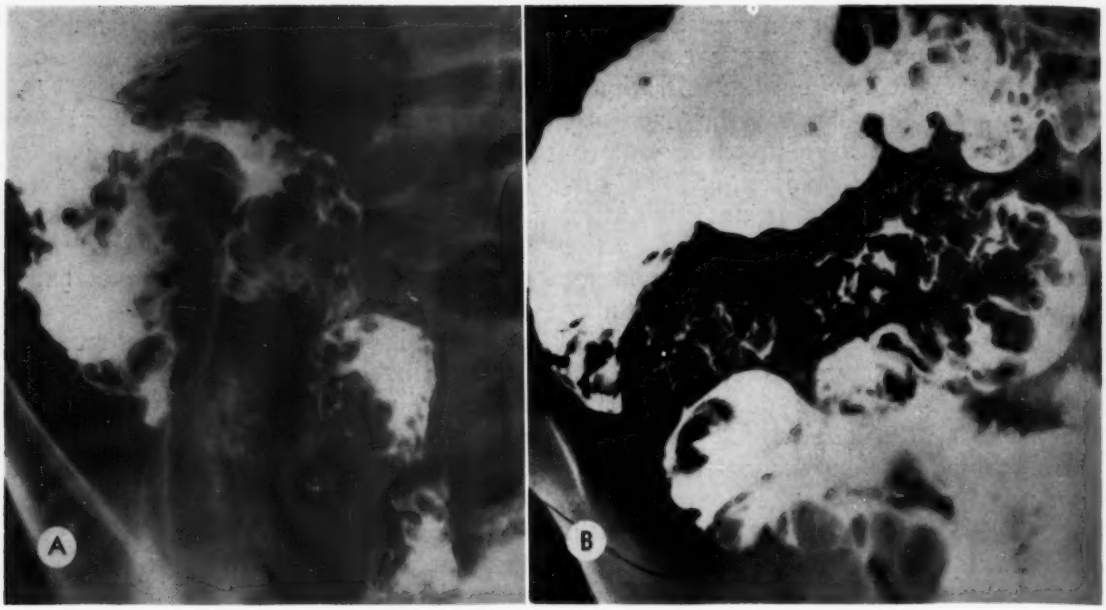

FIG. 1. (*A*) There are multiple tumor nodules of varying size in the terminal ileum, cecum and ascending colon. The terminal ileum is slightly dilated. (*B*) The mucosal pattern is replaced by numerous polypoid intramural and intraluminal defects which alter the caliber of the bowel lumen. There is no evidence of any obstruction.

defects may be obscured by the larger amounts of barium utilized in studying it. In 1 case, the stomach appeared to be involved independently of the small intestinal lesion.

2. *Infiltrating form* (Fig. 2, *A* and *B*; 3, *A* and *B*; 4, *A* and *B*; and 5, *A* and *B*). The bowel wall may become diffusely infiltrated by lymphosarcoma and thickened for considerable lengths. The degree of thickening may vary from area to area, producing irregular segments of narrowing and relative dilatation. The degree of narrowing is never as marked as that observed in carcinoma or inflammations. The mucosal folds may be flattened and effaced, or they may be thickened and thrown up into irregular nodular projections producing coarse, irregular scalloping of the bowel contour with intraluminal filling defects of varying sizes. The mural thickening causes separation and straightening of the bowel loops which stand out clearly from the closely approximated, normal small intestinal loops. The barium column may have a mottled appearance due to increased secretions from within the lumen of the affected segment.

The infiltration may be limited to short segments, either single or multiple, which appear as short areas of eccentric narrowing of the bowel lumen with effacement or thickening of the mucosal folds and evidence of tumor formation. Marked rigidity of the involved segment is not seen nor is there sufficient stenosis to produce dilatation of the small intestine proximally.

Associated with this segmental lesion, small nodular defects along the contour of the bowel lumen are frequently found. They may be situated at some distance from the more conspicuous lesion. They may be single or multiple and are generally less than 1 cm. in diameter. They may widen the normal interval between valvulae but do not extend across the full width of the bowel lumen.

Another form of segmental infiltration of the bowel wall in lymphosarcoma is that which extends for fairly short distances and is accompanied by marked localized dilatation. This has been termed aneurysmal dilatation. The increased thickness of the

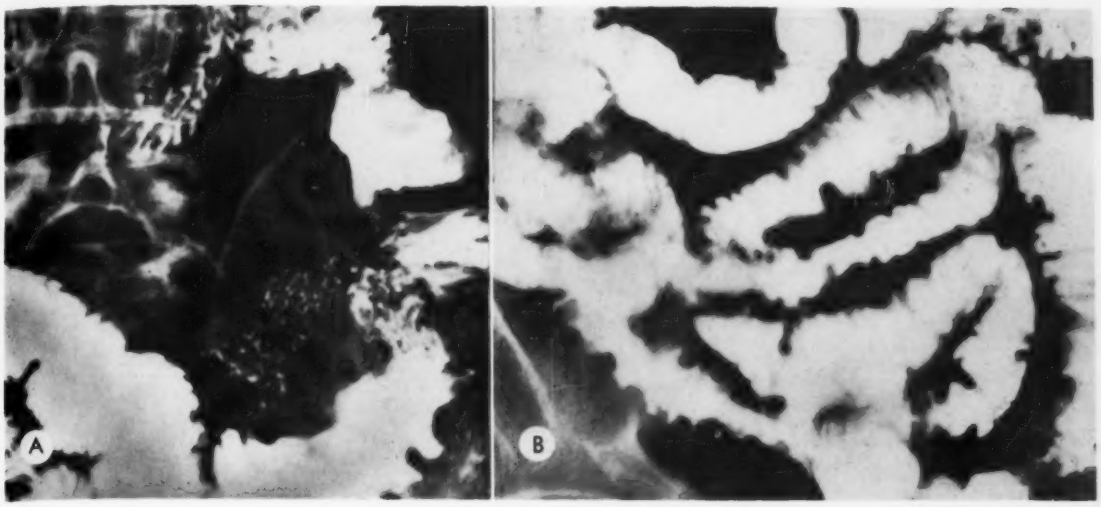

FIG. 2. (*A*) Infiltration of multiple short segments of the jejunum by lymphosarcoma. In this case, two areas are involved. The proximal area of involvement shows a segmental area of irregular dilatation of the bowel lumen, destroyed mucosal folds and a suggestion of an intramural mass. The second lesion, a few inches caudad, shows flattening and rigidity of one wall and abnormal valvular markings on the contour of the opposite wall. (*B*) There is thickening and blunting of the folds with some encroachment upon the bowel lumen but no obstruction. In some areas, small tumor nodules can be identified along the contour of the bowel lumen.

bowel wall is demonstrated by increased separation from adjacent loops. The barium tends to pool within the widened lumen and no mucosal pattern can be seen. The contours of the dilated segment may be smooth, coarsely irregular or show scalloping and nodularity due to intramural tumor formation. The adjacent mucosa may appear intact or thickened and nodular.

3. *Polypoid form* (Fig. 6, *A* and *B*). When the tumor has grown to a size sufficient to produce a discrete intraluminal mass and

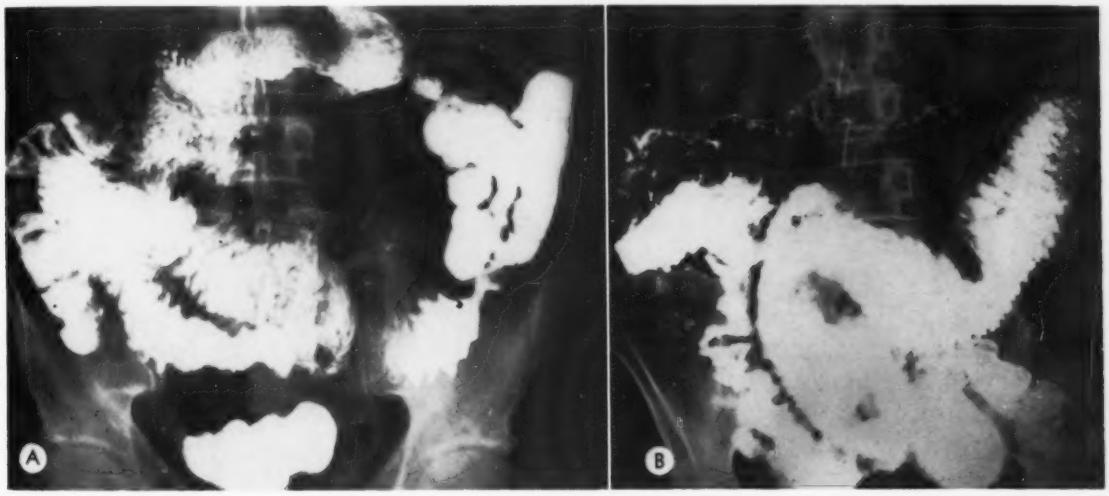

FIG. 3. (*A*) There is slight dilatation of the distal jejunum which shows thickening and blunting of the folds, with effacement in some areas. The contours are coarsely irregular. One short segment of narrowing is seen. This appearance simulates that of the nonstenotic phase of regional enteritis. (*B*) Diffuse infiltrating lymphosarcoma of the jejunum and ileum. In some segments the lumen is dilated with irregular or saw-toothed contours. Elsewhere the folds are thickened.

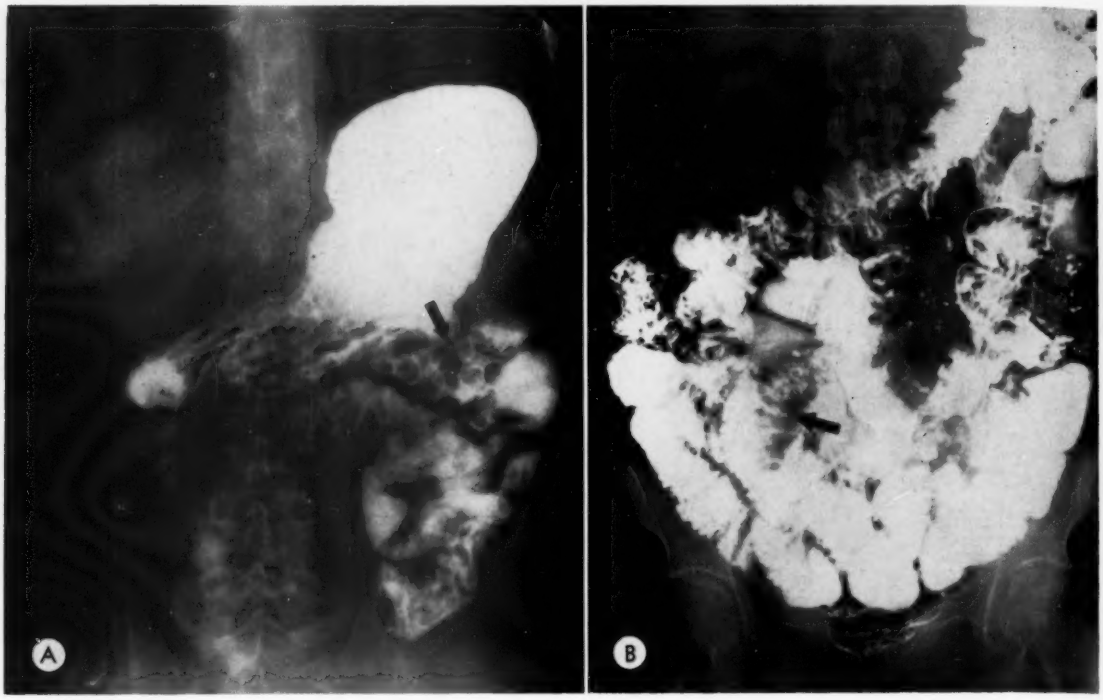

Fig. 4. (*A*) Diffuse infiltrating lymphosarcoma involving the entire small intestine. In the jejunum, multiple intramural and intraluminal tumor nodules (arrow) alter the bowel contour. (*B*) In the ileum, the bowel is dilated. The mucosal folds are thickened and blunted. Mural tumor nodules can still be identified (arrows).

is without intramural extension, it may be drawn forward by peristalsis, forming a pseudopedicle, and may become the lead-point of an intussusception. Unless there are other clues to the nature of the underlying lesion, the cause of the intussusception cannot be determined from the roentgenograms. The polypoid tumor itself is rarely visualized on roentgen study because it is prone to intussusception and may become obscured by the intussusceptum and intussuscipiens.

Four times in this series, intussusception only was seen. In 2 other instances, marked thickening of the mucosal folds in the region of the intussusception and fistulas and nodularity of the adjacent mucosa were noted. In 1 other case, there were multiple polypoid lesions with ulceration of the mucosa, numerous fistulas and dilatation of the involved bowel.

4. *Endo-exoenteric form with excavation* (Fig. 7, *A* and *B*; and 8, *A* and *B*). In this instance, a large excavated mass with multiple fistulas and communications with the adjacent small bowel is seen.

The roentgen findings are usually bizarre. The characteristic finding is an extensive irregular amorphous patch of barium which does not conform to the intestinal lumen and communicates with the surrounding small intestinal loops. The adjacent small intestinal loops are displaced by the large mass. Fistulas are not infrequent.

The earlier changes are seen less frequently. Before massive excavation occurs, the tumor and the involved portion of the small intestine may be criss-crossed by many intercommunicating channels connecting the tumor with the lumen of the small intestine. These channels appear as amorphous barium streaks of varying caliber. In 1 such case, because of the presence of the altered intestinal loops and the fistulas, the diagnosis of regional enteritis was made. Subsequent events leading to massive excavation of the involved area indicated the presence of necrotic neoplasm.

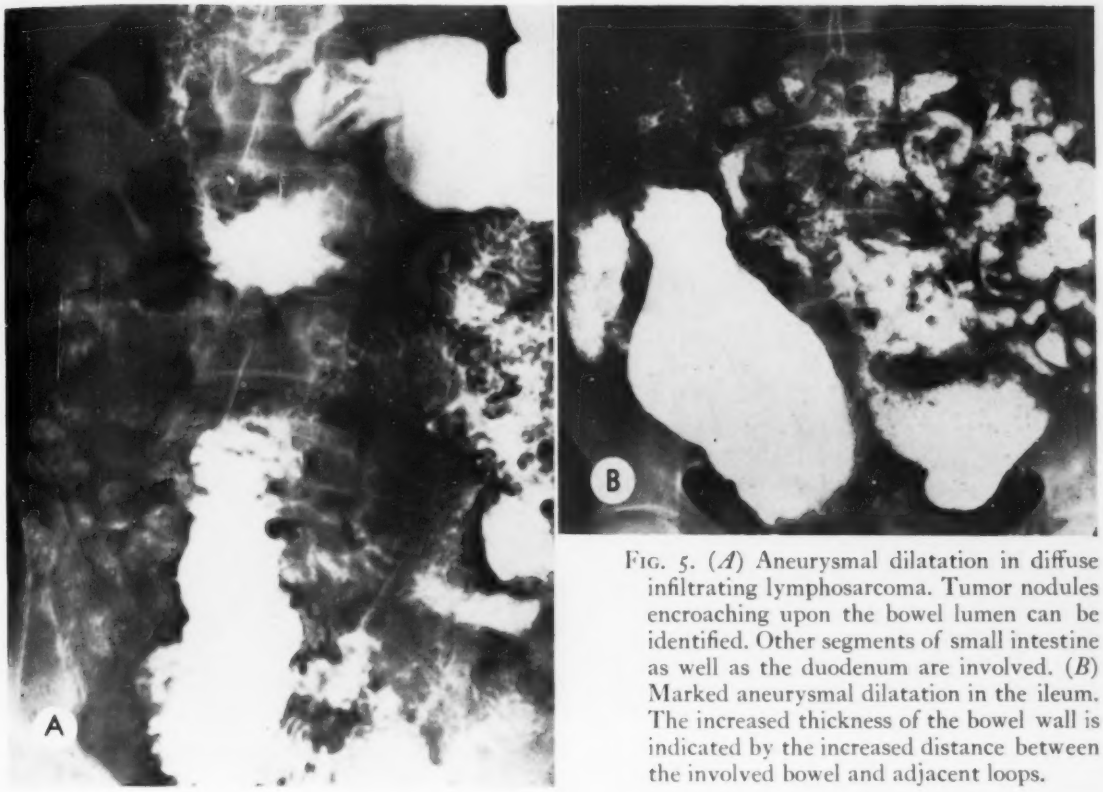

Fig. 5. (*A*) Aneurysmal dilatation in diffuse infiltrating lymphosarcoma. Tumor nodules encroaching upon the bowel lumen can be identified. Other segments of small intestine as well as the duodenum are involved. (*B*) Marked aneurysmal dilatation in the ileum. The increased thickness of the bowel wall is indicated by the increased distance between the involved bowel and adjacent loops.

This appearance is not pathognomonic of lymphosarcoma and has been observed in other sarcomatous tumors of the intestinal tract.

5. *Predominantly invasive form of the mesentery.* (a) Large extraluminal masses. The greater portion of the tumor may grow centrifugally and produce large extraluminal masses which can attain huge proportions and even extend into the retroperitoneum. They manifest themselves roentgenologically by displacement of the abdominal organs, pressure defects upon the adjacent viscera and invasion of the intestinal wall. The presence of a mass alone is not diagnostic of lymphosarcoma unless mural alterations which characterize this type of growth are seen in the small intestine.

It is again of interest to note that in this form of lymphosarcoma, intestinal obstruction is infrequent. In metastatic carcinoma, however, in which there is involvement of the mesentery and infiltration of the bowel, incomplete obstruction is not uncommon.

(b) Production of the sprue pattern (Fig. 9*A*). Along with clinical and laboratory findings of sprue, which can be produced when there is diffuse involvement of the mesentery, a roentgen picture simulating sprue also may be found in lymphosarcoma. Eight such cases have been observed in this series. In 6, the sprue pattern was seen with dilatation of the small intestinal loops, hypersecretion and segmentation of the barium column. The findings were indistinguishable from those seen in idiopathic sprue and a definite diagnosis of lymphosarcoma could not be made. In 2 additional cases, there was evidence of extraluminal masses with displacement and invasion of the small bowel loops superimposed upon the sprue pattern.

DIFFERENTIAL DIAGNOSIS

1. *Hodgkin's disease* (Fig. 10, *A* and *B*). In general, Hodgkin's disease produces the same kind of lesions in the small intestine as lymphosarcoma; however, perforation, fistulas and aneurysmal dilatation have not

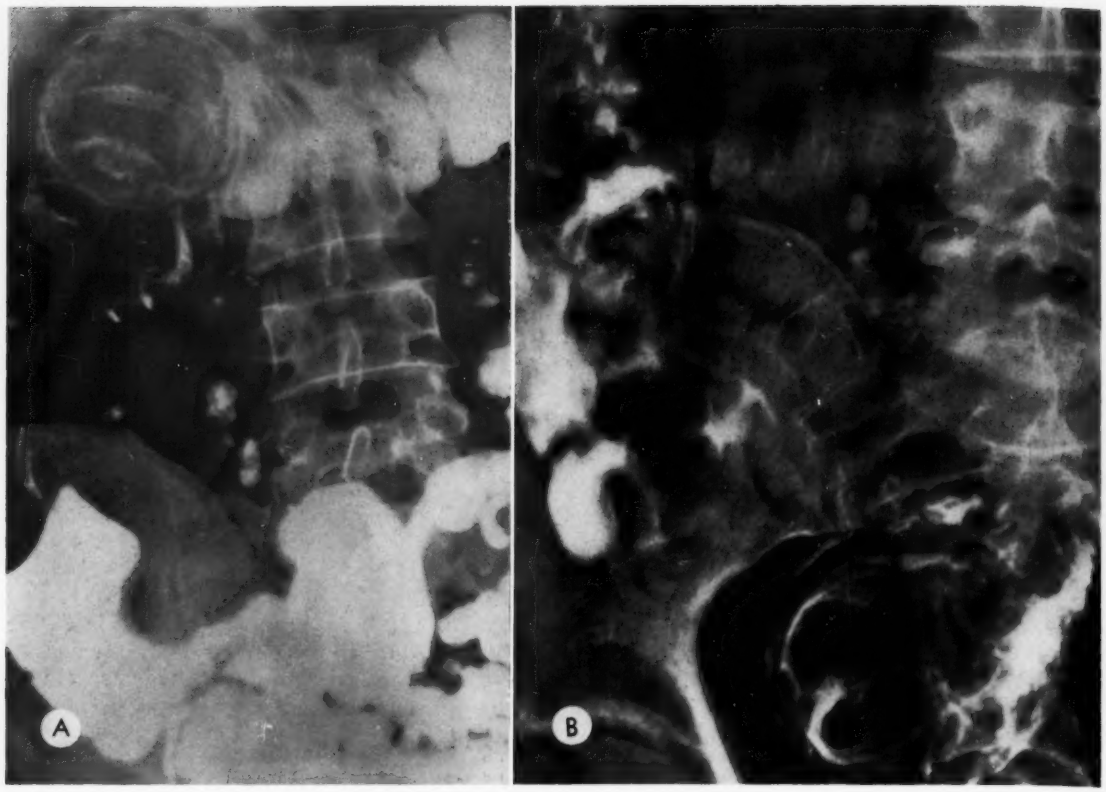

FIG. 6. (*A*) Polypoid lymphosarcoma of the terminal ileum resulting in an ileocolic intussusception with minimal obstruction. The lesion in the ileum is obscured by the intussusceptum. (*B*) Large lobulated polypoid lymphosarcoma of the terminal ileum seen after evacuation of a barium enema.

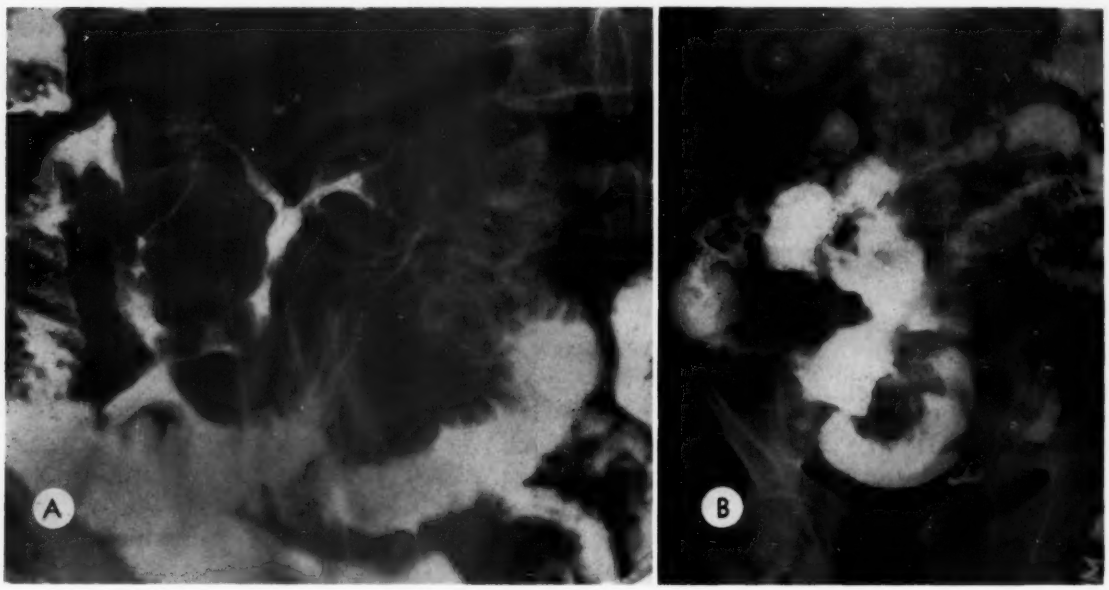

FIG. 7. (*A*) Endo-exoenteric lymphosarcoma of the distal ileum. The normal bowel lumen is replaced by many intercommunicating tortuous tracts through the tumor. The arrow points to the nodular mucosal pattern proximal to the mass. The lumen of this segment is not narrowed. (*B*) Three months later, there is a large irregular, triangular, excavated area within the tumor containing an amorphous collection of barium. The mucosal folds in the adjacent small intestinal loops are considerably thickened.

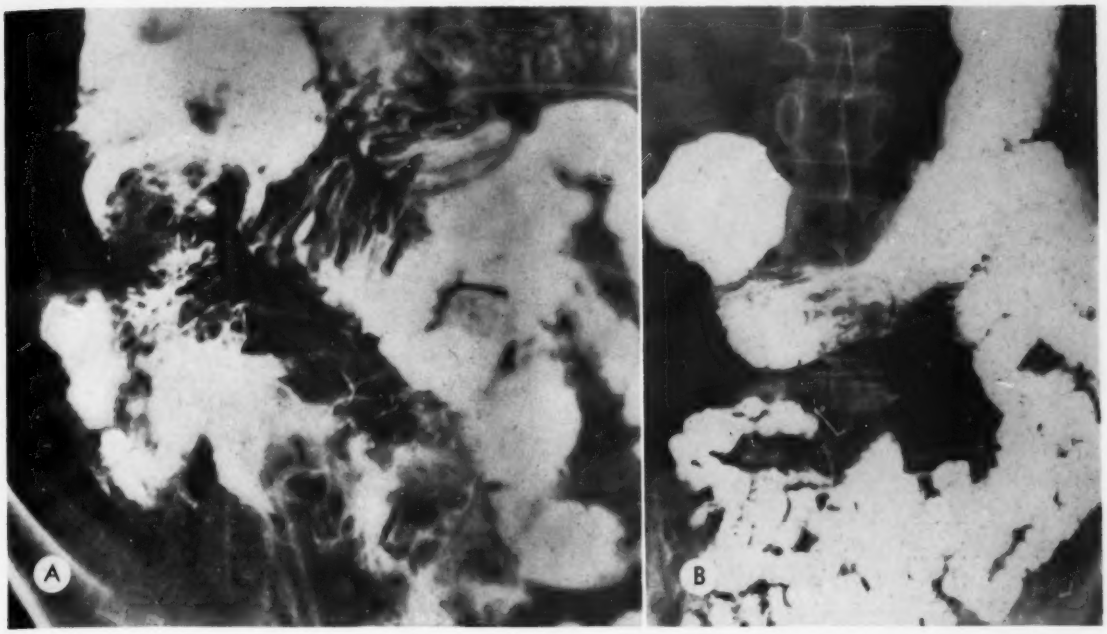

Fig. 8. (*A*) A markedly disorganized pattern produced by multiple polypoid masses with excavation, dilatation and numerous sinus tracts. (*B*) The duodenal bulb is replaced by a large amorphous irregular crater.

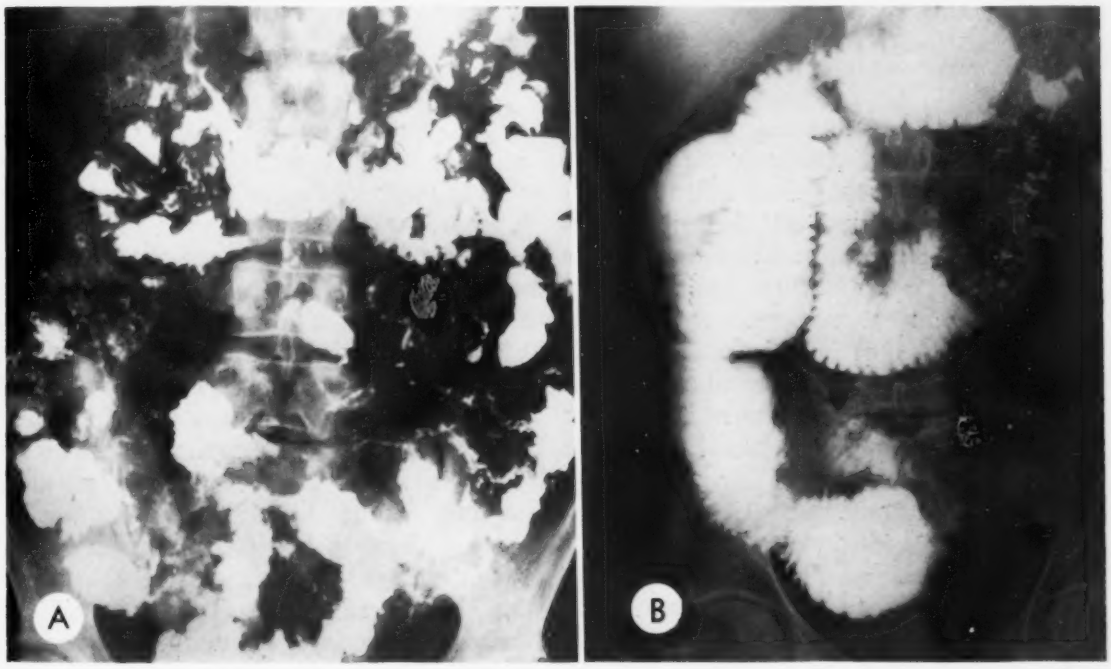

Fig. 9. (*A*) Diffuse lymphosarcoma of the mesentery and retroperitoneum, mimicking the sprue pattern, manifested by segmentation, hypersecretion and flocculation of the barium column. There is no evidence of intrinsic involvement of the bowel wall. (*B*) Unusual instance of obstruction produced by kinking and spasm at the site of an ulcerated intraluminal lymphosarcoma. The lesion was flat and, in itself, did not compromise the bowel lumen.

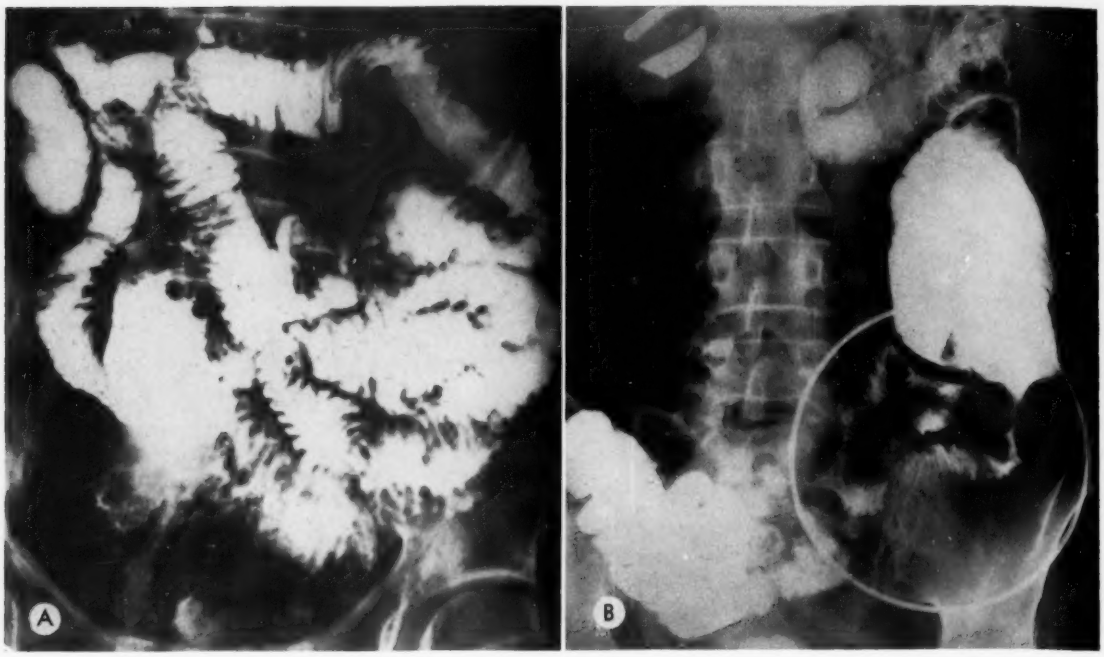

Fig. 10. (*A*) Hodgkin's disease. There are two segments of involvement. Proximally, the lesion simulates a long carcinoma except for lack of obstruction and proximal intestinal dilatation. Distally, the more usual characteristics of a lymphoma are seen with dilatation and perforation. (*B*) Hodgkin's disease of the jejunum. There is a narrow rigid segment producing obstruction to the barium column and dilatation. The contours are scalloped. No overhanging margins are seen. The lumen is eccentric. There is a fairly gradual transition between normal and abnormal bowel.

been as common. Differing from lymphosarcoma, Hodgkin's disease can produce marked fibrosis of the bowel wall with constriction of the lumen. Roentgenographically, there is eccentric narrowing of the bowel lumen, which tapers in a fusiform manner. There are no overhanging edges at the margins of the lesion, which is usually longer than that seen in carcinoma. The contour of the bowel lumen is irregular due to nodularity of the bowel wall. The involved segment may be fairly long. The sprue pattern, multiple small nodular defects and the infiltrating forms have all been seen in Hodgkin's disease. We have seen a single case of leukemic infiltration of the small intestine which appeared as multiple small nodular defects within a short small intestinal loop.

2. *Multiple polyps in the small intestine.* These are rare. When seen, they are usually one of the manifestations of Peutz-Jaeger's syndrome.

3. *Infarction of the small intestine.* An infarcted bowel segment shows progressive changes leading to stricture formation. The findings are similar to those of a benign stricture in other portions of the gastrointestinal tract, namely, a rigid, stenotic segment with a concentric lumen, the margins of which gradually widen to the caliber of the normal adjacent bowel. The margins are exquisitely smooth. Dilatation of the small intestine proximally occurs.

4. *Carcinomas.* These lesions are more common in the jejunum. They are usually short and cause an eccentric rigid lumen, the mucosa of which shows destruction and, occasionally, ulceration. The margins of the lesion are overhanging and obstruction is frequent. The lesions are usually single.

5. *Carcinoids.* Carcinoids occur more frequently in the distal ileum than in other regions of the small intestine. They have the same general appearance as carcinomas. However, on occasion, they may appear as

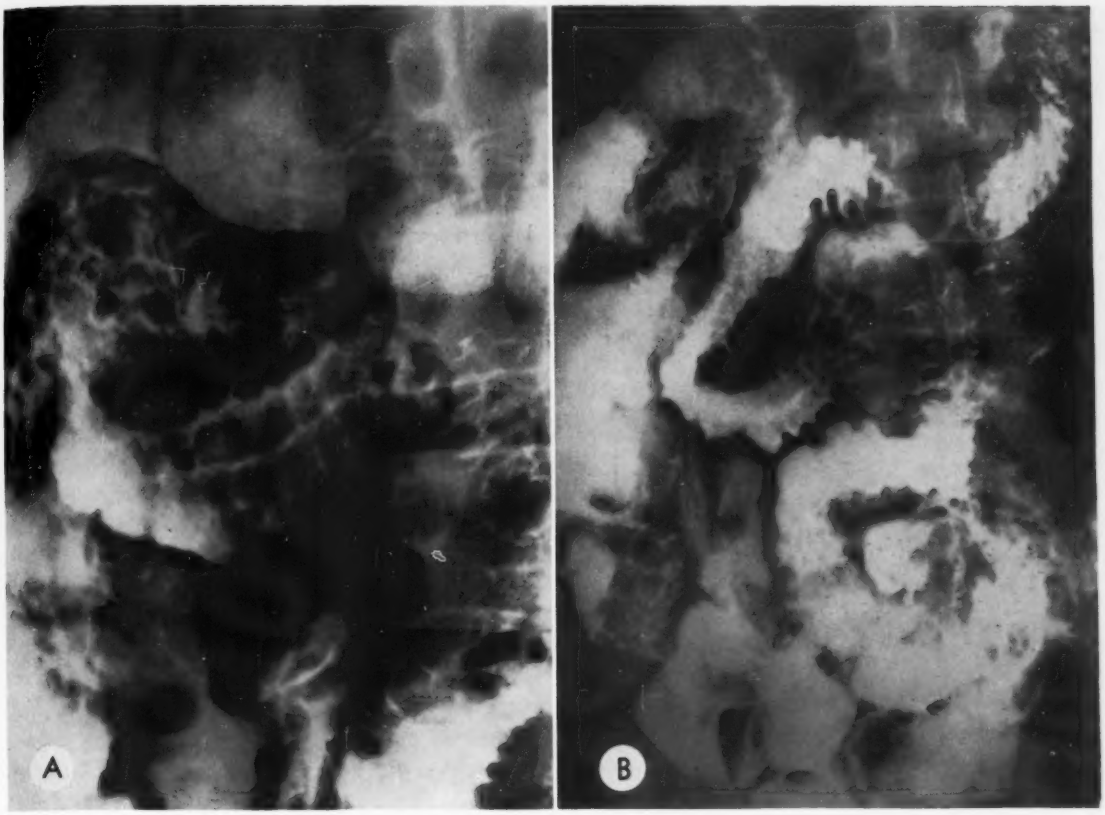

Fig. 11. (*A*) Regional enteritis, nonstenotic form. The mucosal folds are thickened and somewhat nodular in configuration. Linear ulcerations can be identified. (*B*) After an interval, inflammatory polyps appear which vary from tumor nodules in that they are fairly uniform in size, regular in appearance and intraluminal.

a conglomeration of nodular filling defects with some dilatation of the bowel lumen or as multiple isolated nodules with fixation and angulation of the adjacent bowel.

6. *Regional enteritis* (Fig. 11, *A* and *B*). Two thirds of these cases involve the distal ileum. The inflammatory process is characterized by fairly long segments (from 6 to 8 inches to the entire small intestine) of involvement which show linear mucosal ulcerations, inflammatory polyps, fistulas, sinus tracts, separation of the bowel loops due to thickening of the bowel wall and intervening mesentery, skip lesions, spasm, irritability and hypersecretion. On occasion, the nonstenotic phase of regional enteritis can simulate the appearance of diffuse lymphosarcoma of the small intestine. Thickening and blunting of the folds, irregularity of the contour, and intraluminal nodules are features which are common to both. However, in regional enteritis there is more inflammation, producing spasm and narrowing of the bowel lumen.

CONCLUSION

It is always easy to construct a classification and say that this is how to diagnose a particular entity. The small intestinal manifestations of lymphosarcoma are not common and, in their initial stages, are often missed. This has happened to us frequently and re-examination several months later because of persistent symptoms has shown obvious structural abnormalities in the small intestine. There is no doubt that these changes are not always as clear cut as they have been made to seem. On the other hand, in the literature

the prevalent feeling has been that it is rarely possible to diagnose small intestinal lymphosarcoma from roentgen study. This may be so in the individual case where the diagnosis may be extremely difficult. Nevertheless, study of a large number of these cases indicates that the diagnostic outlook is not as bleak as has been considered. The presence of lymphosarcoma can be suggested in a large percentage of cases. It is hoped that, with further study, the earlier changes will be recognized, perhaps altering the grave prognosis of this condition.

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ROENTGEN DIAGNOSIS OF LYMPHOSARCOMA AND RETICULUM CELL SARCOMA IN INFANCY AND CHILDHOOD*

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WHILE the roentgen findings in acute leukemia, neuroblastoma and other of the more common tumors and tumor-like lesions of the young appear to have been fully reported, a similar evaluation of generalized lymphosarcoma and reticulum cell sarcoma apparently does not exist. In fact, only in scattered reports and short references does one find mentioned the various roentgen appearances encountered in this relatively common group of neoplastic diseases of childhood.[5,7,12,17,18,20,28,30,32]

The roentgen diagnosis of lymphosarcoma and reticulum cell sarcoma in adults has been discussed in regard to involvement of bone,[26] thoracic contents[23,31] and the gastrointestinal tract, especially the stomach[16] and small bowel.[9] Because of the somewhat different clinical features these diseases display in children,[24] and in view of the special problems of differential diagnosis which in this age group face the roentgenologist, a more thorough and integrated approach to the roentgen identification of lymphosarcoma and reticulum cell sarcoma in infancy and childhood would seem to be indicated.

MATERIAL

Sixty charts filed under the designation of lymphosarcoma and reticulum cell sarcoma of patients 12 years of age or younger were first reviewed. These were in the period from January 1, 1928, to June 1, 1958. Only cases having histologic proof of lymphosarcoma, reticulum cell sarcoma or follicular lymphosarcoma and having one or more negative bone marrow aspirations were accepted. Consequently, the records of 23 patients who had lymphosarcoma but who also had or developed leukemia were excluded. All acceptable cases had adequate roentgenographic coverage. The total number of patients finally considered suitable for this study was 37. Twenty-four had lymphosarcoma; 12, reticulum cell sarcoma; and 1, follicular lymphosarcoma. Included were 2 patients considered by us to have so-called primary reticulum cell sarcoma of bone.

There were 26 males and 11 females. The mean age at the onset of the disease was 6.2 years with a range from 2 to 12 years. The mean survival rate was 22.3 months, with limits from 1 to 120 months. Ten of the patients are still living. Three of these are living 5.25, 7 and 10 years, respectively, and all are free of disease at present. Eight survived 4 years or longer. Eleven of the 27 patients who died were autopsied.

The diagnosis of lymphosarcoma and reticulum cell sarcoma is, of necessity, a pathologic one, with clinical recognition usually being made possible on the basis of exclusion of other diseases. The diagnosis in these cases was made from biopsy or autopsy material, and all of the histologic slides have been recently reviewed by a staff member of the Department of Pathology. Most of these patients were included in the excellent clinical review of lymphosarcoma in children by Rosenberg *et al.*[24] As they did, we use the term "lymphosarcoma" hereafter to cover the three entities mentioned.

As determined from all possible sources of reliable information, *i.e.*, physical and roentgenographic examinations, biopsy, surgical and postmortem examinations, the

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sites of disease which were identified at one time or another during the course of the illness in the 37 cases are as follows: lymph nodes 25 (cervical 15, mediastinal 16, retroperitoneal 15); pleura 5; bone 10; genitourinary tract (other than kidney) 4; kidney 10; lung 3; gastrointestinal tract 16 (intussusception 6); pancreas 5; gallbladder 2; adrenal gland 3; heart and pericardium 2; tonsil 2; thyroid 2; skin 1; central nervous system 1; adenoids 1; nasopharynx 1; parotid gland 1.

A correlation of these areas of involvement by lymphosarcoma with the ones that were revealed roentgenologically indicated that the radiologist was capable of demonstrating the majority of the lesions by roentgenologic methods. Consequently, the importance of thorough roentgen examination, followed by careful interpretation, is readily apparent in lymphosarcoma.

Charache[3] reported that lymphosarcoma comprised 6.3 per cent of 1,800 malignant tumors in children reported from 7 institutions and 11 per cent of malignant tumors in children studied at the Brooklyn Cancer Institute over a 22 year period. Dargeon[8] noted that lymphosarcoma comprised 5 per cent of 583 malignant tumors in children treated at Memorial Hospital from 1926 to 1950. These compilations and others demonstrate that lymphosarcoma in childhood is not an uncommon form of neoplastic disease.

Rosenberg *et al.*[24] found that the 5 year survival rate in 69 children was 17.4 per cent. Stout[29] observed that in most patients lymphosarcoma may spread rapidly, but occasionally the progress is slow and the disease remains localized for a long period of time. Of 119 cases of lymphosarcoma he reported 12.7 per cent were symptom free after 10 years. Other investigators, Craver,[6] Diamond,[10] Eisenoff *et al.*,[11] Dargeon,[8] Rhoads,[21] and Charache,[3] have reported a few apparent cures. Stout[29] and others[6,8] have emphasized that, when the disease is localized (in other words, when the diagnosis is made early), the response to treatment and the prognosis are better. This points up the importance of roentgen diagnosis in detecting small and early areas of tumor involvement.

ROENTGEN FINDINGS

There were 4 of the 37 patients whose roentgen examinations were negative. These examinations covered the chest, abdomen and bones and the studies spanned periods of time up to 4 years. All 4 patients had local disease in the neck and all are now living.

BONES

The roentgen examinations carried out on the 37 patients revealed 9 with involvement of the osseous system. The bone disease was in 2 categories. Two cases seemed consistent with primary reticulum cell sarcoma of bone,[19] while the larger number was thought to have the generalized type of disease. Cases considered acceptable as primary reticulum cell sarcoma of bone must show no evidence of tumor disease other than the single lesion of bone, as far as can be determined by all appropriate methods of examination. In addition, patients must fail to develop the disease elsewhere for a period of at least 5 months. In a group of 17 cases of this form of the disease previously reported,[26] the youngest patient was 13 years of age and most were 20 or older.

One case of primary reticulum cell sarcoma of bone roentgenographically showed a "mixed type" lesion, *i.e.*, equal amounts of bone lysis and sclerosis (Fig. 1). After radiation treatment, the process became denser and more sclerotic. The second case having a "mixed type" roentgen appearance with periosteal reaction occurred in the distal femur, and it too showed improvement with the development of more sclerosis after irradiation.

Two of the patients having the generalized form of bone involvement presented findings somewhat resembling those commonly encountered in leukemia due to the symmetric distribution of bone destruction in the metaphyseal regions. Both had negative marrow aspirations for leukemia at the

time of the bone invasion. One also presented a localized area of destruction in an os calcis. The transverse bands of diminished density at the metaphyses seen in acute leukemia were absent and the extensiveness of the destruction as well as the degree of sclerosis were both considered to be unusual for leukemia (Fig. 2). Apparently, however, a leukemic type of bone involvement can sometimes be found in patients with generalized lymphosarcoma.

Two children with lymphomatous disease elsewhere showed single osteolytic defects resembling cancer metastases. In another, the involvement was irregularly placed in many bones and was of the "mixed type," while in still another the scattered lesions were slightly sclerotic. The last case, which some might qualify as a primary reticulum cell sarcoma of bone, also showed the "mixed type" roentgen appearance.

Fig. 1. F.O. Primary reticulum cell sarcoma of bone. Solitary, "mixed type" lesion in the femoral shaft. The disease did not become generalized until four years later.

Fig. 2. P.G. Symmetric involvement at the metaphyses of all the large long bones.

This information discloses that the roentgen findings of lymphosarcoma of bone, whether of the primary or secondary variety, are not diagnostically specific. However, as has been pointed out previously,[26] the possibility of this disease being present is suggested when certain roentgen findings are encountered. The hit-and-miss character of the bone involvement, along with evidence of neoplastic involvement in other consistent sites such as lymph nodes, kidneys and gastrointestinal tract, will often suggest the correct diagnosis of generalized lymphosarcoma.

KIDNEY

Two of the 10 patients with known lymphomatous disease of the kidney had no roentgenograms of the urinary tract or abdomen. Six of the 8 who had roentgeno-

Fig. 3. S.S. Marked symmetric enlargement of the kidneys, particularly in the cortical zones.

graphic examination showed bilateral, more or less symmetric enlargement of the kidneys. The enlargement was usually moderate in degree, the kidneys appearing 2 to 4 times their normal size. Most of these patients had more than 1 excretory urographic examination. Two with scout roentgenograms of the abdomen only and 1 with an excretory urogram showed some degree of loss of the kidney outline due to either ascites or massive intraabdominal disease. Obstruction of one ureter and failure to identify any kidney outline were other roentgen findings.

As seen on the pyelographic studies the typical roentgen appearance of lymphosarcomatous invasion was bilateral, fairly symmetric enlargement of the kidney silhouettes, a relative widening of the cortical area and some slight lengthening and thinning of the infundibula of the minor and major calyces. There was no significant alteration in the appearance of the kidney pelvis (Fig. 3). A localized defect marked by local calyceal deformity and enlargement with absence of function developing later presented the only instance of a bulky solitary defect of the kidney due to the tumor. The roentgen appearance in the majority, therefore, bore a close resemblance to that in children with acute leukemia, as has been described.[15]

The patients with kidney involvement had negative laboratory tests for urinary tract disease. In 1 instance, the enlargement disappeared entirely following treatment, the kidneys taking on a normal roentgen appearance (Fig. 4, *A* and *B*). This improvement took place within a 9 month interval. We have observed generally similar roentgen findings and a similar response following therapy in adults.[22]

Lymphosarcomatous involvement of the kidneys in the young must be differentiated roentgenologically from bilateral polycystic disease. The relative widening of the cortex and the absence of any striking degree of calyceal alteration both favor lymphosarcoma. Also, the kidney outline shows no lobulation and the pelvis is not deformed. Response to local irradiation or systemic treatment takes place with lymphosarcoma. Obviously, it is impossible to distinguish roentgenologically between leukemic and lymphosarcomatous disease of the kidneys.

A survey of the literature dealing with lymphosarcomatous involvement of the kidneys revealed only a few reports. However, Ewing[13] found in postmortem examinations that the kidney is a favorite site for lymphosarcoma. He noted that "the deposits may take the form of minute foci, bulky masses or diffuse infiltration." Baldridge and Awe[1] reviewed 150 cases of lymphoma but reported only 1 with lymphosarcoma of the kidney proved histologically. Excretory urography was not done on this patient. Gowdey and Neuhauser[15] reported on 3 cases of acute lym-

phocytic leukemia with kidney involvement. The kidneys, as revealed by excretory urography, showed symmetric and generalized enlargement. Histologically, the nephrons were separated by massive leukemic infiltration, primarily of the cortex. Barney[2] noted kidney involvement in 18 of 23 cases of lymphoblastoma of the urinary tract coming to autopsy. No urographic examinations were done on any of these patients. Freifeld[14] reported a case of lymphoblastoma of the kidney in a 17 year old male. However, this patient had 50 per cent immature cells in the peripheral blood and similar cells also were numerous in the bone marrow. On excretory urography, the kidneys were found to be generally enlarged and microscopic examination at autopsy showed infiltration of the cortex with leukemic cells.

The gross pathologic description of the kidneys in this series was summarized for us by Dr. Stephen Sternberg of the Department of Pathology. He stated that in lymphosarcoma there was no single characteristic or uniform pattern of kidney involvement. However, small and numerous nodular deposits seemed to predominate, although a few times a somewhat localized or bulky mass was found.

FIG. 4. G.C. (*A*) Moderately and symmetrically enlarged kidneys, July 23, 1956. (*B*) Almost normal appearance after treatment, May 8, 1957.

LIVER AND SPLEEN

Enlargement of the liver and spleen were noted roentgenologically only 3 times. Enlargement of the spleen only and of the liver only was present once. The roentgenologist sometimes is able to detect splenic enlargement not clinically evident, because splenomegaly can assume a more or less spherical form, rather than the usual downward enlargement which makes the lower pole easily palpable. However, somewhat to our surprise, it appeared that neither splenomegaly nor hepatomegaly were particularly helpful signs in identifying lymphosarcoma in the young.

LYMPH NODES

Almost 50 per cent of the patients showed

Fig. 5. R.G. Large mediastinal mass due to lymphosarcoma.

roentgen evidence of lymph node enlargement. This was usually in the chest, particularly in the mediastinum (Fig. 5). The roentgen characteristics of lymphoblastomatous involvement in the lymph nodes of the thorax in adults have been thoroughly described and need not be reviewed here. The findings in children are similar.

The abdomen was the next most common site of lymph node enlargement detectable roentgenographically. In confirming this form of lymphosarcoma, a previously negative scout roentgenogram for reference is of great value. Good technique is a major requirement. Obscuration of organ outline, areas of increased density and displacement of known structures are the chief alterations to search for as indicative of lymphadenopathy. Generally speaking, the roentgenologic examination is extremely helpful and in fact a necessity in the evaluation of abdominal masses in children.

Following the scout roentgenogram of the abdomen, the next logical step in the roentgen appraisal of the abdomen in lymphosarcoma is excretory urography. Minor alterations in the position and course of the ureters as seen in the sagittal projection should be interpreted with some caution, because by tracing normal ureters we have found that a fairly wide variation is possible. An abrupt deviation usually is more significant than a smooth, general deviation from the expected normal. Next, the gastrointestinal series, with particular attention to the position and contour of the duodenal loop, may be helpful. Retroperitoneal air injection, aortography and similarly complex studies do not seem to be indicated in children with malignant lymphomas.

Abdominal fluid was suspected in 7 cases, pleural effusion in 5, and in 4 fluid was thought to be present in both of these body cavities.

GASTROINTESTINAL TRACT

The greater incidence of gastrointestinal tract invasion in children as compared to adults has been pointed out.[24] Ten patients roentgenologically showed one or more areas of lymphosarcoma in the gastrointestinal tract. Usually the lesions were polypoid and infiltrating in character, giving the roentgen appearance of cancer (Fig. 6). One aspect to be emphasized is the fre-

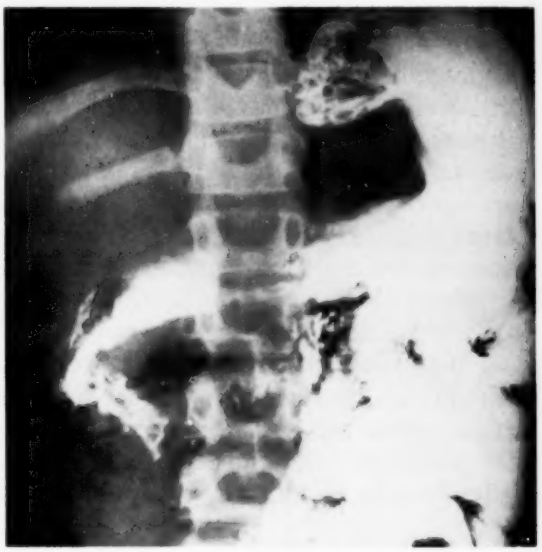

Fig. 6. H.H. Involvement of the second portion of the duodenum. There was an accompanying mass in the right upper quadrant.

quency with which gastrointestinal tract involvement by lymphosarcoma presented as an emergency in this age group. There were 4 patients with intestinal intussusception (Fig. 7) who had roentgenograms available for study, and 2 additional patients presented this symptom complex.

LUNG

The lung is not infrequently involved by lymphosarcoma in adults, but only 5 of these young patients showed this feature as determined by the roentgen findings. Two had rather small, ill-defined, nodular infiltrates, while 3 presented a more patchy or bronchopneumonic-like pattern. Certainly nothing specific about the roentgen appearance of lung invasion by this group of neoplasms was noted (Fig. 8).

OTHER SITES

Some of the more unusual sites of disease were the nasopharynx, ovary, mandible, sphenoid bone and duodenum. In all these areas roentgen evidence of the cancer was present.

Fig. 7. N.T. A mass in the cecum and ascending colon with intussusception.

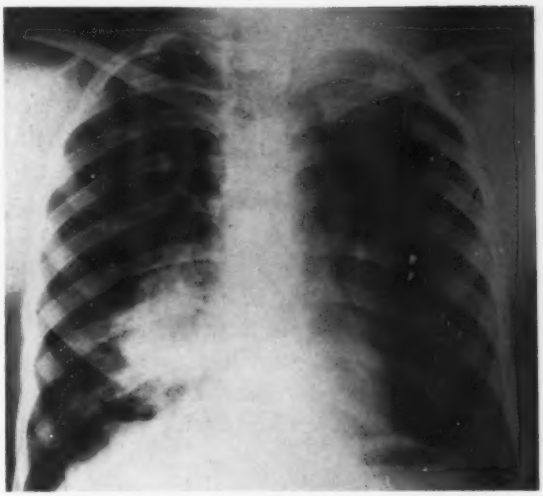

Fig. 8. J.A. An irregular mass in the right lower lung field with lymphadenopathy in the mediastinum and left lower cervical region.

DISCUSSION

There is very little that is specific in the single, localized deposit of lymphosarcoma, wherever it may be located in the body. The somewhat characteristic roentgen appearance in primary reticulum cell sarcoma of bone is encountered infrequently. The findings in the kidney are perhaps more helpful, as they are more often seen. A pattern of symmetric and generalized enlargement would seem to be highly indicative of lymphosarcoma when it is accompanied by roentgen evidence of tumor in other sites. If the kidney involvement is noted alone, then its close resemblance to leukemic invasion of the kidneys would make differentiation between these diseases impossible.

A main point in the roentgen diagnosis of lymphosarcoma, therefore, is that, while one must be acquainted with the appearance of the individual lesion as it involves various organs, the diagnosis is usually made more on the basis of the multiple sites of involvement and their irregular sequence and haphazard arrangement in the body.

Patients who exhibit localized lymphosarcoma clinically, *i.e.*, cervical or axillary lymphadenopathy, should have as a min-

imal roentgen examination a roentgenogram of the chest and a scout roentgenogram of the abdomen, in addition to a thorough study of the local area itself. For those with more widespread disease, skeletal survey, excretory urography and gastrointestinal tract examinations should be carried out. Furthermore, periodic studies of these various regions are indicated because of the tendency of lymphosarcoma to progress and appear in new sites. The chest, skeleton and abdomen are areas where a roentgen survey is most likely to uncover lymphosarcomatous involvement not readily apparent clinically.

Roentgenologically, a differential diagnosis from Hodgkin's disease would be impossible. However, the age limit in lymphosarcoma tends to extend somewhat lower, with Hodgkin's disease in childhood being less common than lymphosarcoma.

Neuroblastoma beginning in ganglionic tissue tends to act more like a primary malignant tumor than one of multicentric origin. Usually the primary site is the adrenal gland. In 40 per cent of the cases the primary focus roentgenologically shows calcification.[25] This fact plus the characteristics of the primary mass will often immediately distinguish this disease from abdominal lymphosarcoma. Calcification with a lymphosarcomatous deposit was not found in this series, even after treatment had been given. In neuroblastoma, the metastases to bone tend to be more frequent and widespread. They are usually symmetric and metaphyseal.[25] This is quite dissimilar to the irregularly scattered distribution of the bone lesions in lymphosarcoma. Generally speaking, therefore, when these two diseases are well advanced, their differential diagnosis is easy.

Wilms's tumor, with its primary involvement of one kidney and its tendency to metastasize to the lungs, yields quite different roentgen findings from lymphosarcoma. The renal findings particularly are conspicuous, because they are almost always unilateral and localized.

The osseous lesions typical of acute leukemia in children are not encountered in lymphosarcoma, although in an occasional instance a slightly similar type of involvement of the bones may occur.[27] It appears, therefore, that most cases of lymphosarcoma, particularly if multiple sites of involvement are present, would be readily distinguishable roentgenologically from acute leukemia.

SUMMARY

1. Thirty-seven proved cases of lymphosarcoma in children have been reviewed in order to determine the roentgen findings in this group of diseases.

2. The roentgen appearance of lymphosarcoma of the kidneys and of primary reticulum cell sarcoma of bone may at times suggest the diagnosis.

3. The correct roentgen diagnosis will usually rest upon the finding of multiple areas of tumor disease in several different organs and the irregularity and asymmetry of the involvement.

4. Children with known lymphosarcoma should always have chest and abdominal roentgenograms, regardless of the location of the primary site or how localized the disease seems to be clinically.

5. Once a bone lesion is detected in lymphosarcoma, a skeletal survey is indicated.

6. Generally speaking, lymphosarcoma, one of the more common neoplasms of childhood, can usually be distinguished roentgenologically from neuroblastoma, Wilms's tumor, leukemia and other neoplasms of childhood, particularly when these diseases are advanced.

7. Six of the cases with kidney disease revealed bilateral, symmetric renal enlargement in spite of negative tests for urinary tract disease and negative bone marrow examinations for leukemia.

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METASTATIC BREAST CARCINOMA SIMULATING ULCERATIVE COLITIS

REPORT OF A CASE

By GILBERT S. MELNICK, M.D., *and* MITCHELL J. ROSENHOLTZ, M.D.
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IN A recent discussion,[14] a variety of types of involvement of the colon by metastatic lesions was presented. We have had occasion to examine the roentgenograms and pathologic specimens of a patient with metastatic disease to the large intestine which showed roentgenographic signs of inflammatory rather than of neoplastic disease.

REPORT OF A CASE

R.R. was a fifty-nine year old white woman who was admitted to the University of Minnesota Hospitals on November 11, 1957.

The patient had had a right radical mastectomy for carcinoma ten years previously. Two years later, because of metrorrhagia, a hysterectomy had been performed.

Five years before admission the patient had developed constant epigastric pain, intensified by heavy meals and relieved by aspirin. This subsided three years later. Diarrhea had then developed, with five to eight defecations per day. At the time of admission the patient was having five bowel movements daily, most frequently at night. There was no pain. Stools were described as watery, without blood or mucus.

For three years the patient had noticed increasing fatigue, weakness and anorexia with at least a fifty pound weight loss. About two weeks before admission she began to notice abdominal swelling and shortness of breath. Swelling of the left lower extremity had been present for one week. For several years she had noticed nodules in the skin.

Physical Examination. Vital signs were normal. The skin was pale. Numerous nodules, from 0.5 to 1.0 cm. in diameter, were scattered over the anterior and posterior trunk and upper arms. These were located predominantly on the right, in the area of the absent breast. Marked abdominal distention was present. There was a midline lower abdominal scar. A reducible hernia was present below the umbilicus. A hard, nodular mass could be palpated through the hernia superiorly and to the right. The mass was not movable and was thought to represent a tumor or intestine involved by tumor. The liver was not palpable. There was evidence of free fluid.

Laboratory Examination. Hemoglobin was 7.0 gm. per cent; white blood cells, 6,000, with a normal differential count; a stool specimen was grossly bloody.

Roentgen Studies. Chest roentgenograms showed an absent right breast, high diaphragm, and extensive osteolytic bone metastases but no pulmonary metastases. Roentgenograms taken during an examination of the colon at another hospital on June 8, 1957 were reviewed (Fig. 1, *A*, *B* and *C*). They were interpreted as showing changes throughout the colon consistent with long standing chronic ulcerative colitis.

Hospital Course. The patient was considered to have metastatic breast carcinoma, but the origin of the abdominal problem was in doubt. The most likely possibilities were metastatic breast carcinoma to the peritoneal cavity, metastatic ovarian carcinoma, or carcinoma of the colon secondary to ulcerative colitis. Therapy consisted of paracentesis, cortisone and stilbesterol. A skin nodule was excised and reported as "metastatic carcinoma of the chest wall, which is of glandular origin and resembles the scirrhous type." Bloody diarrhea continued and because of the onset of hematemesis steroid therapy was halted. Blood transfusions were given as required. The patient continued to decline and expired on December 1, 1957.

Autopsy Findings. Subdermal metastases were noted, many of which were near the mastectomy scar.

Peritoneal carcinomatosis was quite striking. About 75 per cent of the stomach wall was thickened, showing the picture of linitis plastica. There were, in a particularly thickened area just proximal to the antrum, two punched out areas of ulceration in the gastric mucosa, the larger measuring 8 mm. The colon showed a "lead pipe" configuration, having very straight

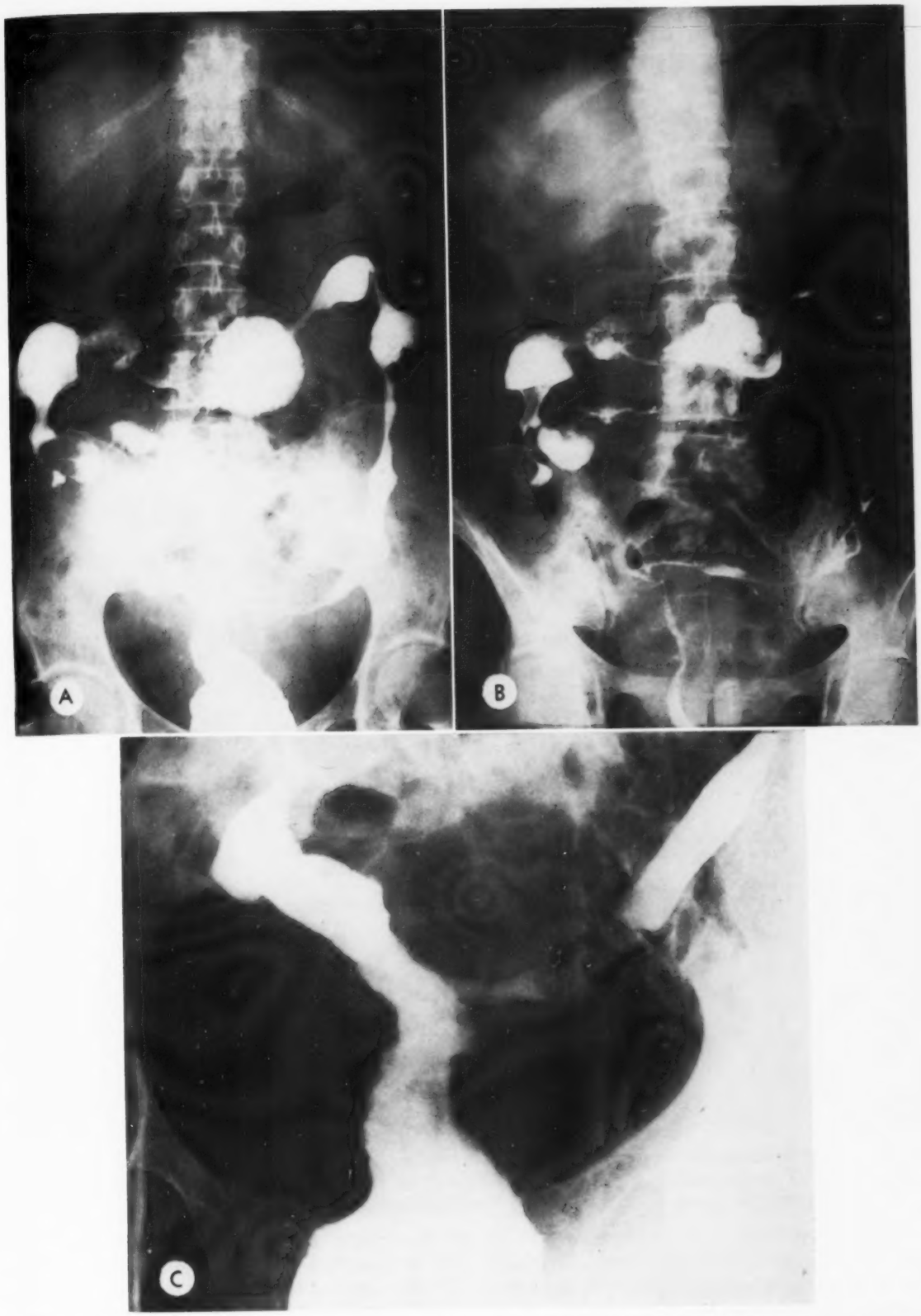

FIG. 1. (*A*) Pre-evacuation and (*B*) post-evacuation roentgenograms of the colon. (*C*) Spot roentgenogram of the rectosigmoid. Typical changes of ulcerative colitis are demonstrated. Note the "ulcerations" in *C*. Lytic bone metastases are present.

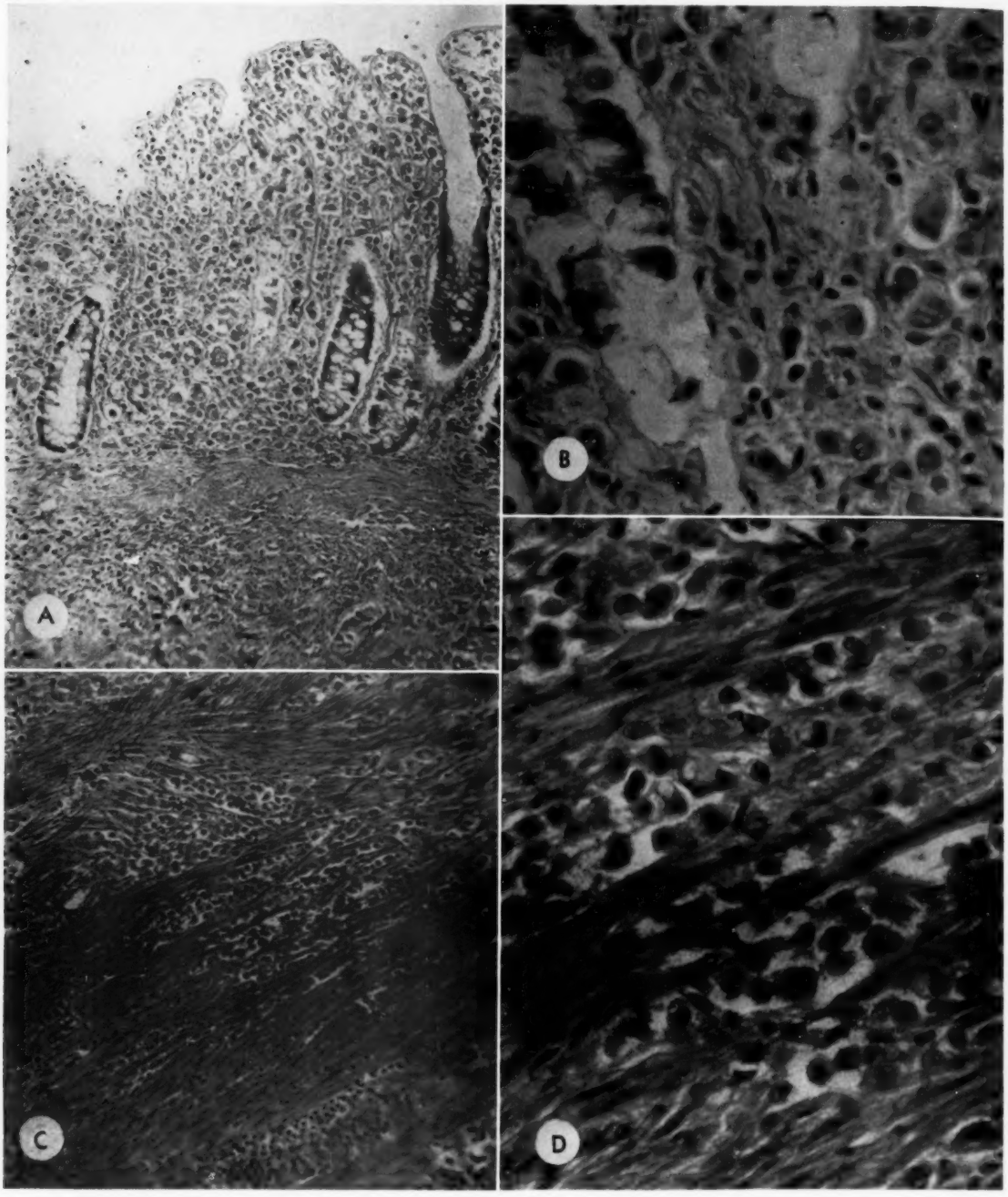

FIG. 2. Photomicrographs of sections of the colon: (*A*) mucosa, ×100; (*B*) mucosa, ×440; (*C*) muscularis, ×100; and (*D*) muscularis, ×440. Note the diffuse tumor cell infiltration of the mucosa and muscle. There are persisting normal glands which are autolyzed but do not show the changes of ulcerative colitis.

and obviously shortened segments. The lumen was small, approximately 1 cm. in diameter throughout, but the wall was markedly thickened, up to as much as 8 mm., from the cecum to a point well below the peritoneal reflection. The mucosal lining appeared smooth and shiny.

The microscopic changes in the colon (Fig. 2, *A-D*), stomach, and bladder were quite comparable in that each showed diffuse infiltration of the mucosa, submucosa and muscle by malig-

nant epithelial cells, for the most part separate one from the other. Some of the tumor cells contained cytoplasmic vacuoles which displaced the nucleus to one side to form "signet-ring" cells. None of the colon sections showed changes compatible with ulcerative colitis.

Other sites of metastases included numerous lymph node chains, the left breast, visceral pleura, liver, spleen, left kidney, bladder, peritoneum, retroperitoneum, bone marrow and right ovary. There was bilateral hydronephrosis, more marked on the left, apparently related to external ureteral compression by neoplastic involvement of the retroperitoneum.

DISCUSSION

Lesions of the colon having the gross appearance of linitis plastica and a microscopic picture of diffuse epithelial tumor cell infiltration of the mucosa, submucosa and muscle have been described. Our perusal of the literature revealed 5 such lesions interpreted as primary carcinoma in the colon[7,13] and 17 interpreted as unusual metastases from gastric carcinomas of the linitis plastica type.[1,3,4,6,9,11,12] Only 4 cases have been described which, in our opinion, represent metastatic carcinoma to the colon from the breast.[3,4,5]

In 1909, Faroy[2] probably noted the first such case, a forty-one year old woman who had had vague gastric complaints for one year. At autopsy there was a 6 cm. hard mass, which was fixed to the skin, in the right breast. There were numerous subcutaneous nodules as well. The colon showed some patchy areas of narrowing associated with thickening of the wall, while the stomach grossly demonstrated striking thickening of the walls. The microscopic examination of the stomach, the only organ studied by microscopy, showed neoplastic cells in the mucosa and submucosa.

The second case described as metastatic carcinoma from the breast was that of Jørgensen in 1935.[5] His patient showed a linitis plastica pattern in the stomach, segments of the colon, the ureters and the rectovaginal septum. Microscopically, he found these tissues, as well as the myocardium, infiltrated by large, well-circumscribed, tumor cells. He stressed that these cells stained positively with mucicarmine and infiltrated the involved structures without producing a significant reaction in the surrounding tissue.

Fischermann[3] has recently described 2 other cases of metastatic carcinoma of the breast, one infiltrating the muscle of the stomach and the second the muscle layers of the stomach, rectum, sigmoid colon, uterus, and uterine tubes. In each of his cases the patient's chief complaint was some variant of "dyspepsia." Jørgensen's patient, too, in addition to noticing the presence of a breast mass, complained first of fatigue, diarrhea, and "gastric influenza," with vomiting, at least fourteen months before her death. In Fischermann's second case a colostomy had been performed nine months prior to death for what was mistakenly thought to be a primary carcinoma of the rectum. In our case also, the patient had had diarrhea for three years prior to death, that complaint being, in retrospect, the first definite sign of metastatic carcinoma.

The roentgenographic findings in this instance very accurately simulated those of advanced ulcerative colitis, namely, loss of the normal mucosal pattern, loss of haustral markings and decrease in the size of the colon, both of the lumen and the over-all length. A variation of the shortened, narrowed colon, called the "linked sausage appearance" in Bockus' text,[10] was also seen in this case. Interestingly, though the roentgen appearance was that of multiple, minute ulcerations, especially demonstrated on the spot roentgenogram of the rectosigmoid, none were actually present. Presumably, this roentgen finding was produced by the fixed buckling of the mucosa secondary to the involvement of the entire thickness of the colonic wall by metastatic tumor.

Similar roentgen appearances of linitis plastica in the colon have been reported. In the first case of Laufman and Saphir[7] there had been a long (twenty-three year) history

of ulcerative colitis. Therefore, though the pathologic findings were of diffuse scirrhous carcinoma, it would have been impossible to determine whether the colitis or the carcinoma caused the roentgen changes. Karstens and Bargen[6] reported 2 cases without a clinical history of ulcerative colitis that showed roentgen findings of ulcerative colitis. In both, operation revealed extensive scirrhous carcinoma involving the stomach and colon. On a statistical basis it was likely that the primary disease was in the stomach in both cases. Sussman[12] similarly reported 2 cases of coincident carcinoma of the stomach and colon with the primary most likely in the stomach.

Our case, then, might represent a primary carcinoma of the stomach, colon or breast. The over-all duration of the patient's disease and the appearance of nodules in the skin, some in the mastectomy scar as well as in distant sites, support the premise that this was primary in the breast, especially since there was a history of breast carcinoma. Thus, this is the fifth reported case of metastatic carcinoma from the breast with the unusual clinical, roentgenologic and morphologic changes described.

SUMMARY

A case of metastatic carcinoma of the breast with unusual visceral metastases is described. The roentgenologic changes in the colon are indistinguishable from those of chronic ulcerative colitis.

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We wish to thank Dr. James R. Dawson and Dr. Harold O. Peterson for their valuable criticism and suggestions. This case is published with the permission of Dr. B. J. Kennedy of Minneapolis and Dr. J. P. Medelman of St. Paul, Minnesota.

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Vol. 86, No. 4

NEW ROENTGENOLOGIC SIGNS OF CARCINOMA OF THE URETER*

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IN PYELOGRAPHY, as so often happens in clinical medicine, no absolute yardstick exists by which to differentiate minor variations of normal from minor or early changes of the abnormal. We are forced to evaluate the variations in each segment of the urinary excretory tract and try to determine whether the minor alterations seen on roentgenograms are significant enough to support the presumptive clinical diagnosis.

Our study is an attempt to evaluate the present concepts for early diagnosis of ureteral carcinoma, and to illustrate certain specific changes which we have found helpful.

When faced with a patient presenting the clinical symptoms of painless or recurrent hematuria, it must be axiomatic that the intravenous pyelogram must not be considered normal unless the entire ureter is completely and satisfactorily visualized from the renal pelvis to the ureterovesical junction. The greatest cause of misdiagnosis is the labeling of an intravenous pyelogram as normal when the entire ureter is not visualized; what appears to be an area of peristalsis may, in fact, be a ureteral defect.

In our series, we have seen 4 apparently normal intravenous pyelograms on which the ureter above and below the lesion revealed no evidence of dilatation, but at the site of the lesion a short segment of the ureter was not visualized. For an adequate evaluation retrograde pyelography must be performed when space defects in the ureter are observed on intravenous pyelograms.

We would like to present two findings of carcinoma of the ureter not previously emphasized:

1. The kidney and ureter above the site of the ureteral tumor may be entirely normal. Most textbooks[3,5] emphasize the presence of severe hydronephrosis or a nonfunctioning kidney as the primary finding in ureteral carcinoma. The degree of hydronephrosis is simply an expression of the degree of obstruction produced by the lesion and therefore small and occasionally large lesions may produce almost no ascending obstruction. One cannot correlate the degree of obstruction with the size of the tumor but, in general, later stages of the disease will be more likely to present obstruction. In our series, as previously stated, approximately one-half of the cases presented normal appearing upper urinary tract and ureters on intravenous pyelograms.

2. On the retrograde study, we have observed a peculiar coiling of the catheter which occurred just below the site of the lesion. The mechanism of this coiling will be explained later.

In a previous publication[1] we noted that with the development of more adequate diagnostic techniques, the clinical recognition of ureteral tumors has become less difficult. Primary neoplasms of the ureter, formerly considered rare, have been recognized in ever increasing numbers.[11] Senger and Furey[9] state that 86.5 per cent of tumors of the urinary epithelium occur in the bladder, while 8.4 per cent occur in the renal pelvis and ureter. Foord and Ferrier[2] calculate that about 1 per cent of carcinoma in the upper urinary tract originates in the ureter.

In the history of this lesion, Rayer of France described the first case in 1842; however, it was not till 1878 that the first

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histologically proved case was reported by Wising and Blix. As recently as 1934[4] only 68 acceptable ureteral malignancies were reported, but by 1955 this number had risen to 333 as reported by Savignac.[7] It is safe to assume that the present number is well over 500 cases.

Seventy-five per cent of ureteral neoplasms are carcinoma while 21 per cent are classified as benign papillomas. This is questioned, as many pathologists consider all urinary tract papillomas as papillary carcinoma Grade 1. The remaining 4 per cent constitute the rare group of sarcomas, hemangiomas or fibromas.

Renner[6] uncovered only 3 cases of primary ureteral neoplasm in 13,000 necropsies at the Vienna Pathological Institute. Two cases were found in 1934 at Johns Hopkins Hospital in 22,000 urologic admissions. At Bellevue Hospital between 1904–1935, only 1 case was reported in 22,810 autopsies, and at the Chicago Cook County Hospital between 1930–1951, only 4 cases were reported in 26,400 necropsies.

Before discussing our cases, we would like to review briefly the pathogenesis and symptomatology of ureteral carcinoma.

The etiology of ureteral epithelial tumors is unknown, but it is closely related to that of renal and vesical epithelial tumors. All theories pertaining to the genesis of carcinoma in other systems also apply here. They occur primarily in males (66 per cent) between the fourth to seventh decades with 75 per cent occurring in the lower third of the ureter.

The most frequent findings and symptoms are hematuria, pain, a palpable mass in the renal area and a mass defect visualized on the pyelogram.[10] Hematuria is present in approximately 75 per cent of cases, a palpable mass (hydronephrotic kidney) in 40 per cent and pain, secondary to distention of the ureter, in approximately 50 per cent of cases. In most of the reported series of cases, the correct preoperative diagnosis was made in approximately 50 per cent.[8] We feel that with an awareness of the clinical picture and proper utilization of intravenous and retrograde pyelography, the diagnostic accuracy can be markedly improved.

We have mentioned two diagnostic aids; namely, the importance of visualizing the entire ureter since smaller lesions which are nonobstructing will present a normal sized ureter and kidney as in 4 of our cases, and the coiling of the catheter at the site of the lesion (Fig. 1*A*). To our knowledge, this latter finding has never been previously described. We explain its mechanism as follows:

In the case of mechanical obstruction of the ureter, such as occurs by a calculus, the ureter below the site of the obstruction would tend to collapse (Fig. 1*B*). Following obstruction by an expanding intraluminal tumor mass, such as a primary ureteral carcinoma, the lumen of the ureter directly above and below the lesion will gradually expand due to tumor growth. Upon passing a retrograde catheter, we have observed that the size of the lumen directly below the tumor is increased sufficiently so that when the catheter is impeded by the tumor mass, it tends to coil within the lumen, and will either remain at this site or, after coiling, pass above the tumor mass. This characteristic coiling occurred in approximately half of our cases and has been of considerable aid in suggesting the presence of an expanding lesion of the ureter.

REPORT OF CASES

CASE I. A fifty-seven year old female (the only female in our series) had gross hematuria several times over a period of one year. Her original work-up was for hemorrhagic cystitis and retrograde pyelography was reported as normal. A subsequent intravenous pyelogram, one year later, was "normal" except that the lower half of both ureters did not visualize (Fig. 2). A retrograde pyelogram at this time (Fig. 3) revealed a defect in the middle third of the right ureter with an essentially normal upper tract. The lesion proved to be a papillary carcinoma (Fig. 4).

CASE II. A seventy-one year old male was admitted with hematuria and symptoms of sepsis one month previously. Intravenous pyelogra-

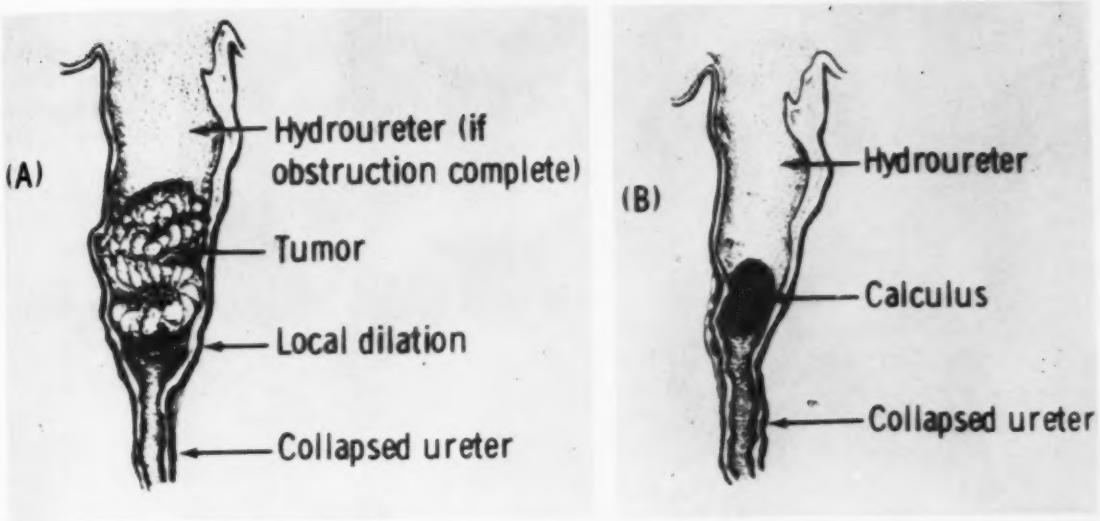

Fig. 1. Case 1. (*A*) Localized dilatation of the ureter below the tumor allowing space for catheter coiling. (*B*) Collapsed ureter below calculus.

Fig. 2. Case 1. Essentially normal intravenous urogram, but the lower half of the ureter is not visualized. Note the absence of hydronephrosis and hydroureter.

Fig. 3. Case 1. Retrograde urogram revealing filling defect in the middle third of the right ureter. Again note the absence of dilatation above the lesion.

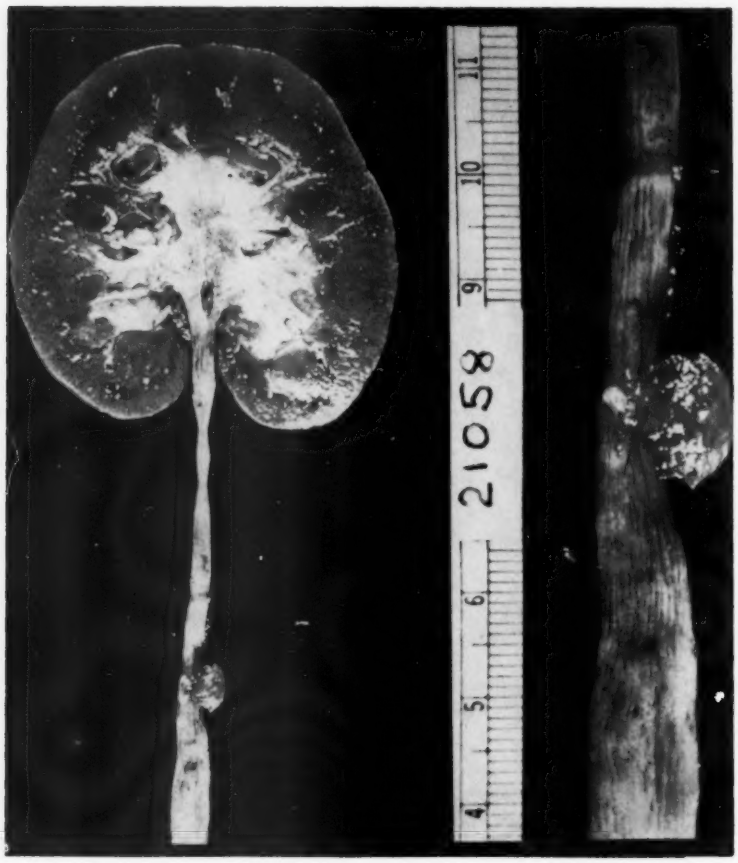

FIG. 4. Case I. Surgical specimen of the papillary carcinoma in the middle third of the ureter. Note the completely normal kidney and ureter above the tumor.

phy revealed a poorly functioning left hydronephrotic kidney. Retrograde pyelograms disclosed the typical coiling of the catheter at the site of the lesion (Fig. 5 and Fig. 6). At surgery an intraluminal papillary carcinoma with associated marked hydroureter and hydronephrosis was found (Fig. 7).

CASE III. A fifty-three year old male was admitted because of gross painless hematuria. Intravenous pyelography revealed no function on the left side. The right side was normal. A cystoscopy disclosed a lesion at the ureterovesical junction preventing retrograde pyelography of this side. At surgery a large papillary carcinoma with associated hydroureter and hydronephrosis was found (Fig. 8).

CASE IV. A sixty-three year old male presented himself with a three week history of right lower abdominal colicky pain and gross hematuria. Retrograde pyelograms demonstrated the typical coiling effect (Fig. 9). There was hydroureter and hydronephrosis above this. At surgery the lesion was found to be a large fungating intraluminal papillary adenocarcinoma of the lower third of the ureter with marked hydroureter in the segment proximal to the lesion (Fig. 10).

CASE V. A sixty-three year old male presented a three day history of hematuria and mild pain on the left side of the abdomen. An intravenous pyelogram appeared essentially normal, but the lower third of the left ureter did not visualize. Retrograde pyelograms revealed the typical coiling of the catheter (Fig. 11); the upper tract appeared normal (Fig. 12). Surgery revealed a lesion which had caused slight dilatation of the ureter, just above the tumor, but the rest of the ureter and kidney was normal. On histopathologic study this proved to be a papillary carcinoma (Fig. 13). Four and one-half years after the original ureteral surgery, the patient returned and examination showed a solitary superficial bladder metastasis.

Case vi. A forty-eight year old male was admitted with right flank pain and hematuria of two months' duration. The upper urinary tracts were essentially normal on intravenous pyelograms. A small cupping defect was noted in the mid-portion of the right ureter on one roentgenogram (Fig. 14).

A retrograde pyelogram revealed large filling defects of the lower third of the right ureter with an essentially normal ureter and kidney above the lesion (Fig. 15). On histopathologic examination a papillary carcinoma was found (Fig. 16).

Case vii. A fifty-nine year old male presented gross painless hematuria of several days' duration. An intravenous pyelogram was reported as normal (Fig. 17) but the lower ureter was not visualized. Cystoscopy revealed a papillary carcinoma of the lower ureter, protruding from the orifice.

PATHOLOGY

Primary tumors of the ureter can be subdivided into two main groups; namely, (A) epithelial and (B) mesodermal. These can be further subdivided into (1) malignant and (2) benign.

Fig. 5. Case ii. Catheter exhibits typical coiling at the site of the tumor.

Fig. 6. Case ii. Marked hydroureter and hydronephrosis above the lesion are visualized. The tumor causes a filling defect at the pelvic segment of the left ureter.

A.(1) Primary malignant epithelial tumors are classified as (a) papillary carcinoma of low grade malignancy, (b) papillary carcinoma of high grade malignancy, and (c) infiltrating type. These tumors are usually unilateral, with approximately two thirds occurring in the lower third of the ureter. They metastasize more rapidly than other similar bladder tumors because of the greater lymphatic supply of the ureter and the thinness of the ureteral wall, allowing for quicker permeation. The usual sites of metastases in order of frequency are regional lymph nodes, liver, lumbar verte-

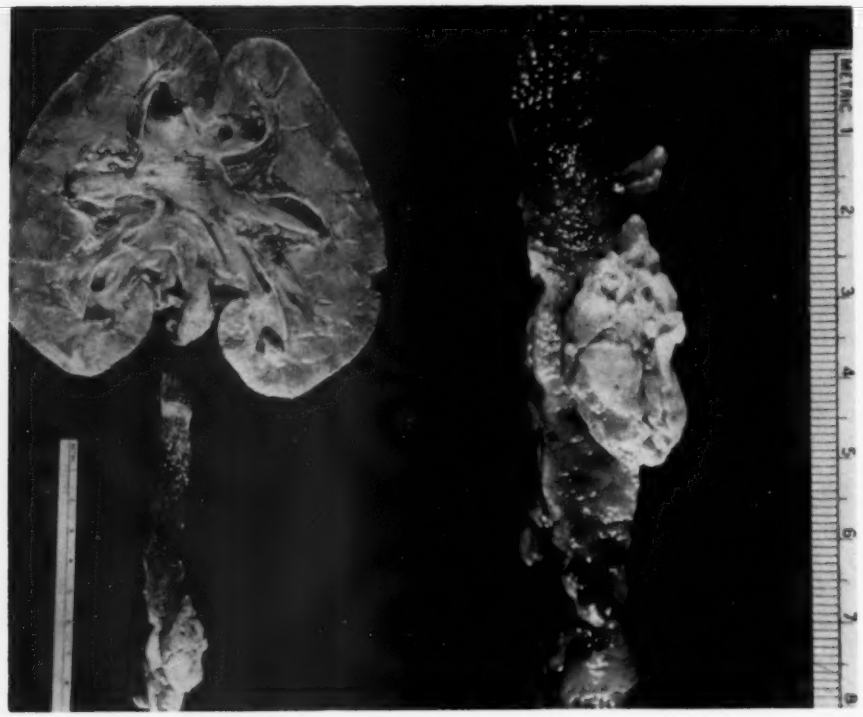

FIG. 7. Case II. Surgical specimen of the papillary carcinoma with marked hydroureter and hydronephrosis.

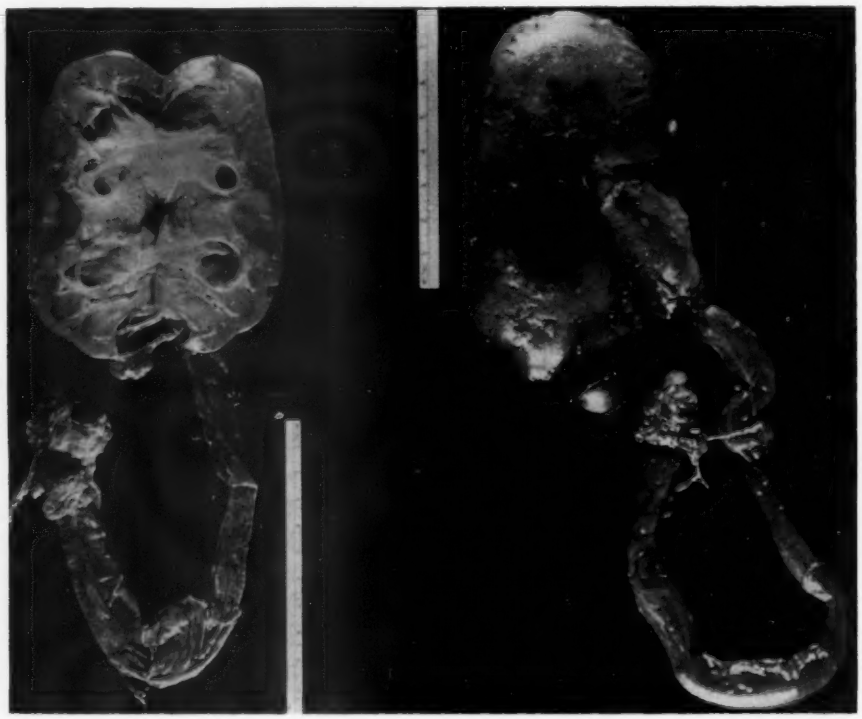

FIG. 8. Case III. Surgical specimen of the large papillary carcinoma at the lower end of the left ureter with associated hydronephrosis and hydroureter.

Fig. 9. Case IV. Coiling of the ureteral catheter with localized dilatation of the ureter at the site of the lesion, and a filling defect and cupping are visualized.

brae, lungs, kidney and adrenal glands.

A.(2) The true benign tumors of the ureter consist of polyps, of which 72 cases have been reported in the literature.[8] The so-called benign papillomas are classified by many pathologists as malignant lesions.

B.(1) Primary malignant tumors of mesodermal origin include the sarcomas which are exceedingly rare and have a very grave prognosis.

B.(2) Benign mesodermal tumors such as fibromas and endometriosis of the ureter are extremely rare.

Fig. 10. (below) Case IV. Surgical specimen of the papillary adenocarcinoma showing dilatation proximal to the lesion.

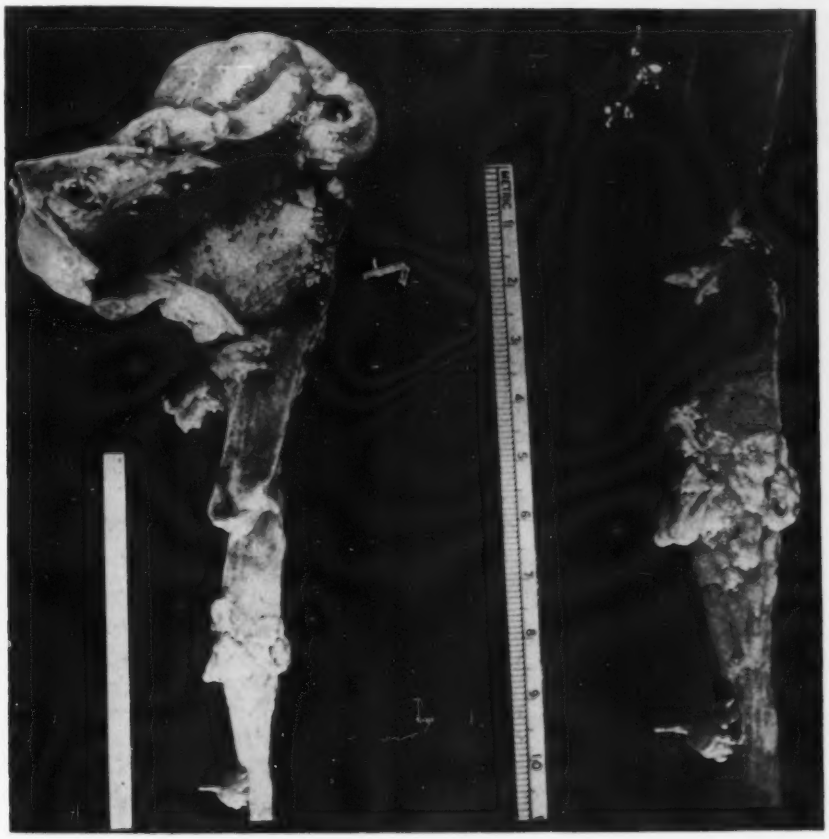

FIG. 11. Case v. Retrograde pyelogram showing the typical coiling of the catheter at the site of the lesion.

PROGNOSIS

Because of the small number of cases and inadequate follow-up, a true evaluation is difficult. It is generally accepted that any patient living more than four years has a favorable prognosis.[8] In our series, one case is alive nine years and several are approaching five years. Only one is dead.

TREATMENT

The best treatment has proved to be radical surgery. Radiation therapy has not been effective either in the primary or metastatic lesion.

The type of surgery performed depends on the patient's general condition, extent and location of the tumor, the presence or absence of metastases and the condition of the opposite kidney. A total nephro-ureterectomy and a partial cystectomy is the usual preferred treatment. When radical surgery is not indicated or cannot be performed, other types of surgery which can be helpful are simple nephro-ureterectomy, resection of the tumor with end to end anastomosis and local reimplantation

FIG. 12. Case v. Retrograde study revealing a normal ureter and kidney without dilatation above the lesion. A filling defect and localized dilatation in the ureter at the site of catheter coiling are also visualized.

Fig. 13. Case v. Surgical specimen of the papillary carcinoma of the lower third of the left ureter.

Fig. 14. Case vi. Intravenous urogram showing no evidence of hydroureter and hydronephrosis. Cupping of the margins of the ureter at the site of the lesion at the level of L-5 is visualized.

Fig. 15. Case vi. Retrograde study showing a filling defect and cupping of the ureter at the site of the tumor. Note again the lack of dilatation above the lesion.

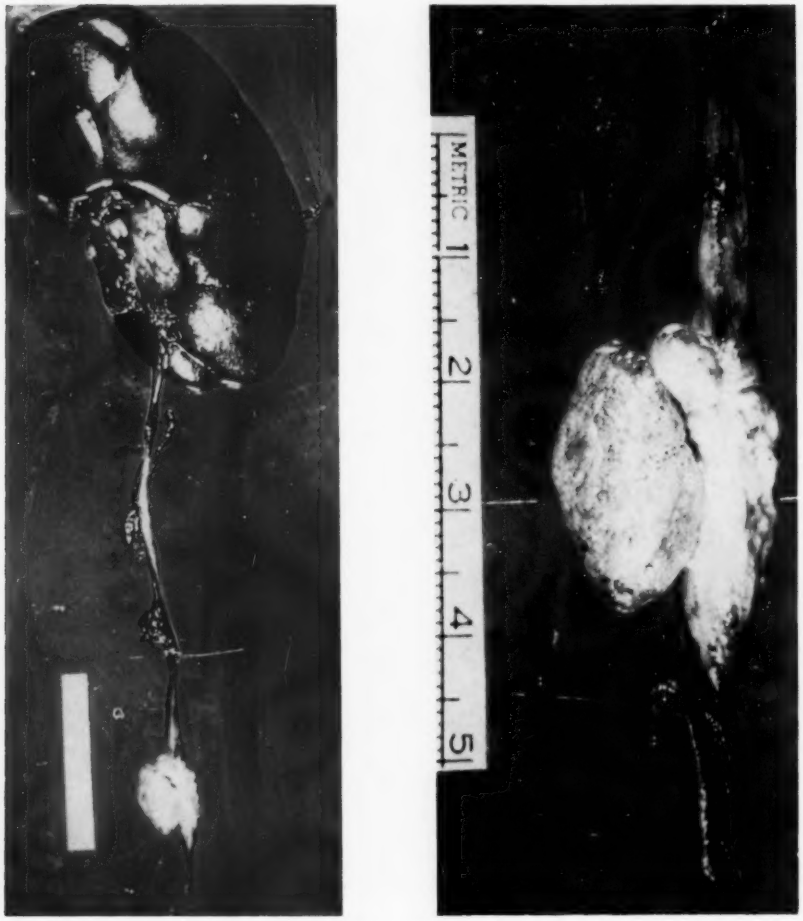

FIG. 16. Case VI. Surgical specimens of the papillary carcinoma and normal kidney and ureter.

of the ureter into the bladder or renal pelvis.

Secondary ureteral tumors involve the ureter by direct extension from neighboring organs, occasionally by metastatic emboli from distant organs and by metastatic implants via the urinary route from the kidney or bladder.

SUMMARY

1. The classic clinical and roentgenologic findings of primary carcinoma of the ureter, stressing two signs which we have found of value in early diagnosis, are presented.

2. The diagnostic triad most often emphasized by all authors consists of gross hematuria, often painless, occurring in the fourth through seventh decades of life; hydronephrosis or nonfunctioning kidney revealed by intravenous pyelography; and a mass lesion in the ureter constituting a filling defect with marginal cupping at the lower and upper ends of the lesion.

3. In analyzing our 7 cases, we have been impressed by the number of normal appearing intravenous pyelograms. This stresses the importance of adequate and complete visualization of the entire ureter in every case of gross hematuria. Nonvisualized segments of the ureter attributed to peristaltic waves must therefore be re-evaluated in the light of our findings. Retrograde pyelography is often required. Hydronephrosis and nonfunctioning kidneys are manifestations of the disease at a later stage when the lesion has progressed to such an extent as to cause partial or complete obstruction.

4. Coiling of the ureteral catheter just

Fig. 17. Case vii. Intravenous urogram with essentially normal findings except for nonvisualization of the lower two inches of the ureter just proximal to the ureterovesical junction.

below the lesion occurs on a mechanical basis, and, when present, is highly suggestive of an expanding intraluminal mass, usually carcinoma. This diagnosis can be suggested even before the instillation of contrast medium.

5. These findings are emphasized in the hope that primary carcinoma of the ureter will be considered in every case of hematuria, and that earlier diagnosis will therefore be made.

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VENA CAVAGRAPHY IN THE MANAGEMENT OF MALIGNANCY*

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THE extent and location of malignant disease are two of the most important factors influencing the choice between curative and palliative therapy. Visualization of the superior and inferior venae cavae can show pathology in the mediastinum and the retroperitoneal space that is missed by the more commonly employed roentgenographic procedures. These great veins, which are readily deformed by adjacent pathology, are easily and safely visualized with contrast material. A simplified technique of vena cavagraphy will be illustrated and representative cases presented from over 400 studies.

Cavagrams are of particular value in cases of lymphoma, where the clinical staging is of the utmost importance in determining initial and subsequent therapy.[1,2] Accurate staging is not possible without adequate evaluation of the mediastinal and retroperitoneal lymph nodes. Occult malignancies in the retroperitoneal area, suspected clinically, can often be revealed by inferior vena cavagraphy because of the large number of lymphatic nodes surrounding this great vein. Pathologic enlargement of the right adrenal gland, right kidney, liver, and head of the pancreas can be detected by this technique. Evaluation of therapeutic results in retroperitoneal disease and determination of the need for further therapy are greatly aided by this objective method of evaluation.

ANATOMIC CONSIDERATIONS

Although only fifteen per cent of the retroperitoneal space is occupied by the inferior vena cava, the majority of the retroperitoneal lymph nodes are concentrated along the course of this great vessel. The right adrenal gland, right kidney, liver and head of the pancreas are in intimate contact with it (Fig. 1). The thin wall and low hydrostatic pressure of the inferior vena cava permit this structure to be easily deformed, displaced or obstructed by adjacent masses. Normal inferior vena cavagrams are illustrated in Figure 2. Of sig-

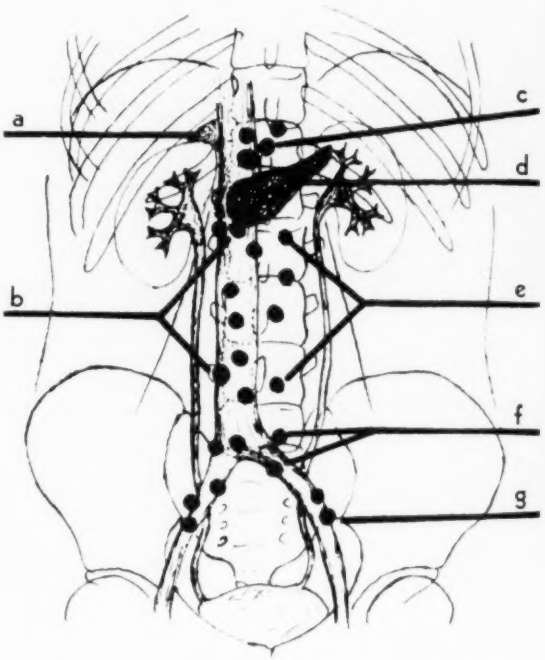

FIG. 1. Schematic diagram of the major relationships of the inferior vena cava. The right lateral aortic lymph nodes surround the vena cava. (a) Right suprarenal gland; (b) right lateral aortic lymph nodes; (c) main mesenteric lymph nodes; (d) pancreas; (e) left lateral aortic lymph nodes; (f) subaortic and common iliac lymph nodes; (g) external iliac lymph nodes.

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The opinions expressed are those of the authors and do not necessarily represent those of the Medical Department or the Department of the Navy.

Fig. 2. Normal inferior vena cavagrams. (1) Variation in the course of the vena cava as it lies in the fossa venae cavae on the posterior surface of the liver. This may be a shallow groove or may be a canal covered by a thin portion of the hepatic substance. (2) Change in width of the vena cava and the irregularity in the contrast column at the insertion of the right and, to a lesser extent, the left renal vein. (3) Smooth pressure defect produced by the right renal artery as it courses posterior to the vena cava near the L2 level. (4) Normal defect due to compression by the right common iliac artery.

nificance is the widening, dilution and apparent irregularity of the column of contrast material at the level of the renal veins. At the origin of the inferior vena cava, compression by the right common iliac artery normally produces a defect which should not be interpreted as pathologic. The influx of blood from the ipsilateral internal iliac vein and the contralateral common iliac vein may also produce an

TABLE I

NORMAL MEASUREMENTS OF THE INFERIOR VENA CAVA*

Level		L_4	L_3	L_2	L_1	D_{12}	D_{11}
Distance from the posterior border of the inferior vena cava to the anterior border of the vertebral body (lateral view)	Average	−2.6	−1.2	3.0	4.0	3.6	14.8
	Range	−11–0	−8–2	−6–11	−5–16	−2–10	0–35
Distance from the lateral margin of the inferior vena cava to the middle of the vertebral body (anteroposterior view)	Average	35.2	36.3	38.8	44.4	42.2	42.4
	Range	25–41	25–45	25–46	27–55	28–55	25–54
Diameter of the inferior vena cava (lateral view)	Average	18	20	20	23	25	28
	Range	10–29	14–30	19–30	14–32	19–34	20–35
Diameter of the inferior vena cava (anteroposterior view)	Average	28.4	28.5	29.0	33.2	31.0	26.4
	Range	24–33	24–36	25–37	26–45	24–43	18–37

* All measurements are in millimeters. Negative va'ues refer to the millimeters of overlap of the vena cava on the vertebral body.

irregularity in the contrast column. The right renal artery indents the posterior aspect of the inferior vena cava as it courses to the kidney. The caudate lobe of the liver indents the left margin of the vena cava at the D_{11}–D_{12} level. The normal measurements of the vena cava at its various levels are given in Table 1.

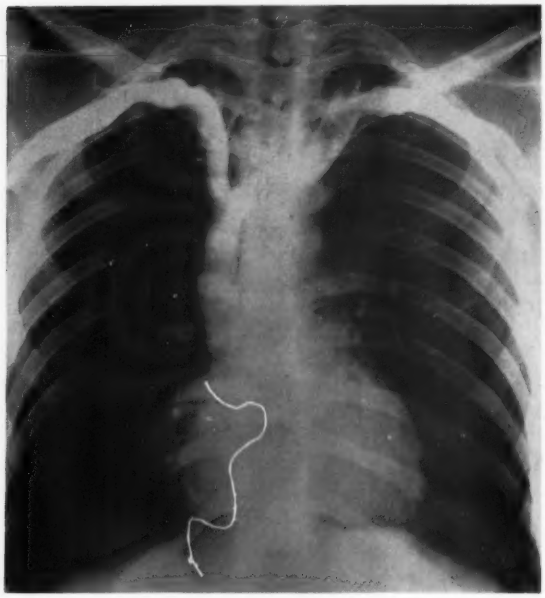

FIG. 3. Normal superior vena cavagram with the major tributaries. The advisability of utilizing the left antecubital vein is illustrated by the course of the left innominate vein across the mediastinum. This bilateral injection was done for illustration.

The superior vena cava and the innominate veins are intimately related to most of the lymph nodes and other structures of the superior mediastinum. The left innominate vein traverses the entire width of the superior mediastinum; therefore, visualization of the superior vena cava via its tributaries on the left is more informative than right sided injection (Fig. 3; 13, *A* and *B*; and 14, *A*, *B* and *C*).

TECHNIQUE

The technique of superior and inferior vena cavagraphy differs from intravenous pyelography primarily in the site and speed of injection and timing of the film exposures. Superior vena cavagraphy is a simple procedure performed by the rapid injection of 30 cc. of 50 per cent hypaque into a left medial antecubital vein, with the patient supine. A No. 18 gauge needle is utilized and while the patient takes a deep, slow breath the injection is completed within five seconds. This can be a unilateral or bilateral injection. The first film of the chest is exposed at the end of injection. A second film is exposed six seconds later to evaluate obstruction and collateral circulation.

A simplified technique of inferior vena

cavagraphy has been described in previous publications.[5,6] The technique consists essentially of the rapid injection of contrast material into the right femoral vein with the left femoral vein occluded and the head of the table elevated ten degrees. The injection is made during the expiratory phase of respiration. A No. 17 gauge needle is utilized. It is advisable that a bevel no sharper than 45 degrees be used to facilitate threading of the needle and to minimize the possibility of extravasation. Films of the abdomen are exposed in both anteroposterior and lateral projections. Following these injections pyelograms are taken. Figure 4 illustrates the simplicity of the technique.

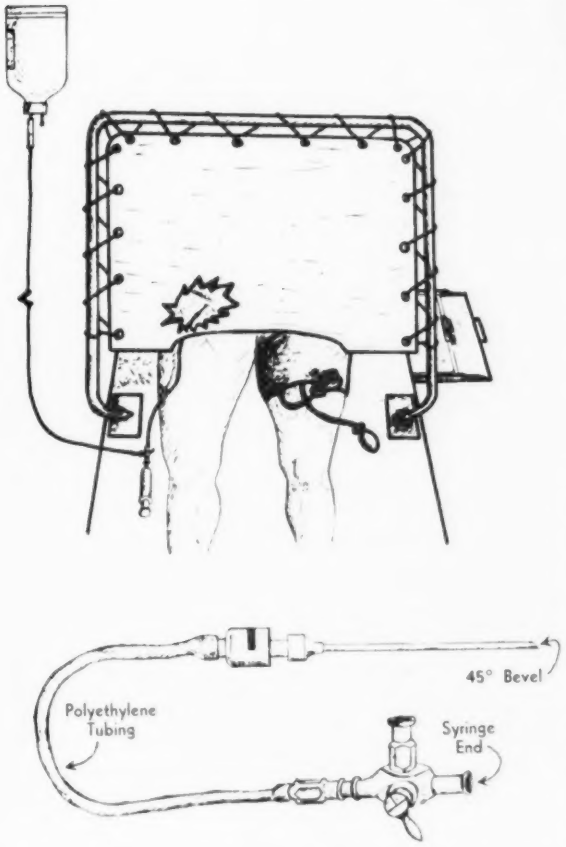

Fig. 4. Diagram of the technique of inferior vena cavagraphy. The sphygmomanometer is inflated to decrease the dilution of the contrast material by blood from the contralateral lower extremity.

CLINICAL APPLICATION

In the past four years over 400 vena cavagrams have been performed at the U. S. Naval Hospitals, Pensacola, Florida, and St. Albans, New York, to aid in the management of patients with malignant disease of various types. These studies are of particular value in cases of lymphoma where the clinical staging of the disease is of utmost importance in determining initial therapy. Accurate clinical staging of lymphoma is not possible without adequate evaluation of the mediastinal and retroperitoneal lymph nodes. When inferior vena cavagraphy demonstrates retroperitoneal lymphadenopathy, intensive therapy to the mediastinal and/or peripheral lymph nodes would needlessly deplete the patient's gen-

Fig. 5. (*A*) The inferior vena cavagram illustrates a sharply localized, large, extrinsic pressure defect at the D12 to L_3 level. The intravenous pyelogram was normal. (*B*) After a 3,400 r tumor dose to this well-defined retroperitoneal region, the inferior vena cavagram was normal and remained so for the following year. Adequate radiation therapy was thus delivered to a smaller portal; irradiation of a larger field or the use of chemotherapy was unnecessary. Either one of these techniques would have depleted the body economy needlessly.

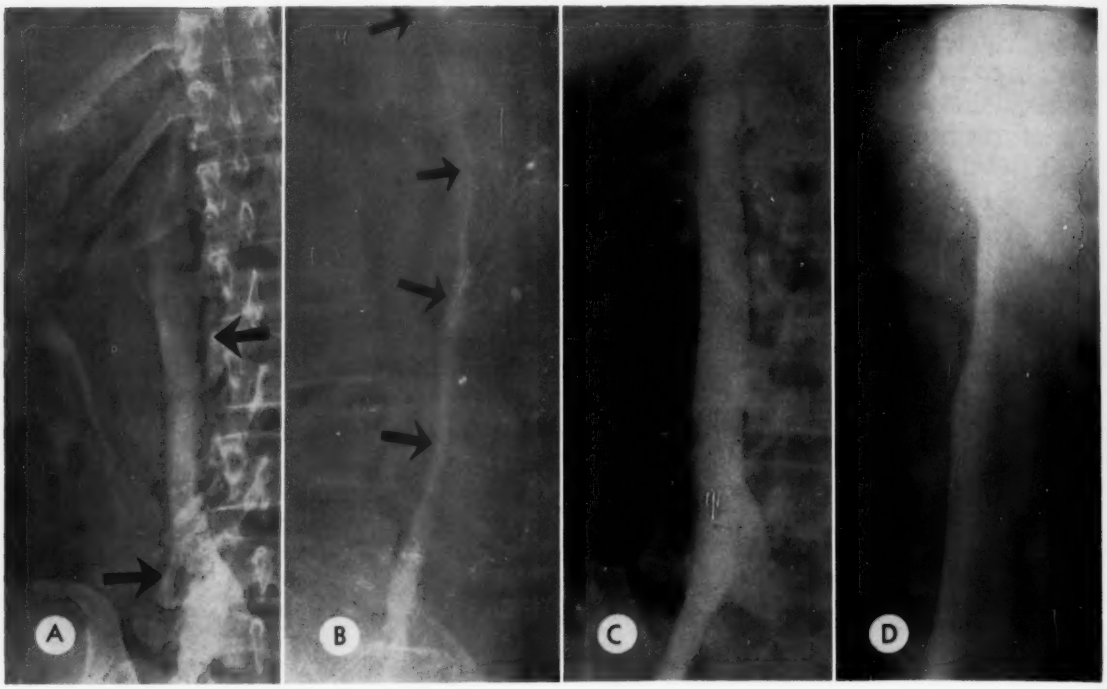

FIG. 6. (*A* and *B*) Massive lymphadenopathy posterior to and surrounding the inferior vena cava is well illustrated in the lateral projection. In the anteroposterior projection the high grade obstruction at the L_1–L_2 level is evidenced by the filling of the right ascending lumbar vein (upper arrow in *A*) and its tributaries (lower arrow in *A*). Deviation of the inferior vena cava is also seen in this projection. In the absence of a Valsalva maneuver, the demonstration of collateral circulation on an inferior vena cavagram is pathognomonic of a complete or incomplete obstruction more cephalad. (*C* and *D*) Inferior vena cavagrams following a 3,500 r tumor dose delivered through opposing fields to the entire abdomen. Note the marked improvement in the configuration of the vena cava, the absence of visualized collaterals, and the need for localized radiation therapy to the L_1–L_2 level, which was given subsequently.

FIG. 7. Giant follicular lymphoma of the left cervical region was diagnosed by biopsy four years before present admission for malaise and weight loss. (*A*) The inferior vena cavagram demonstrates partial obstruction at the L_3-L_4 level with collaterals consisting of both right and left ascending lumbar veins. Distortion at L_1-L_2 indicates other lymph node involvement. (*B*) Following a 3,000 r tumor dose to the L_1-L_5 region in forty-one days, dramatic symptomatic improvement occurred. A calcified uterine fibromyoma is present in the pelvis.

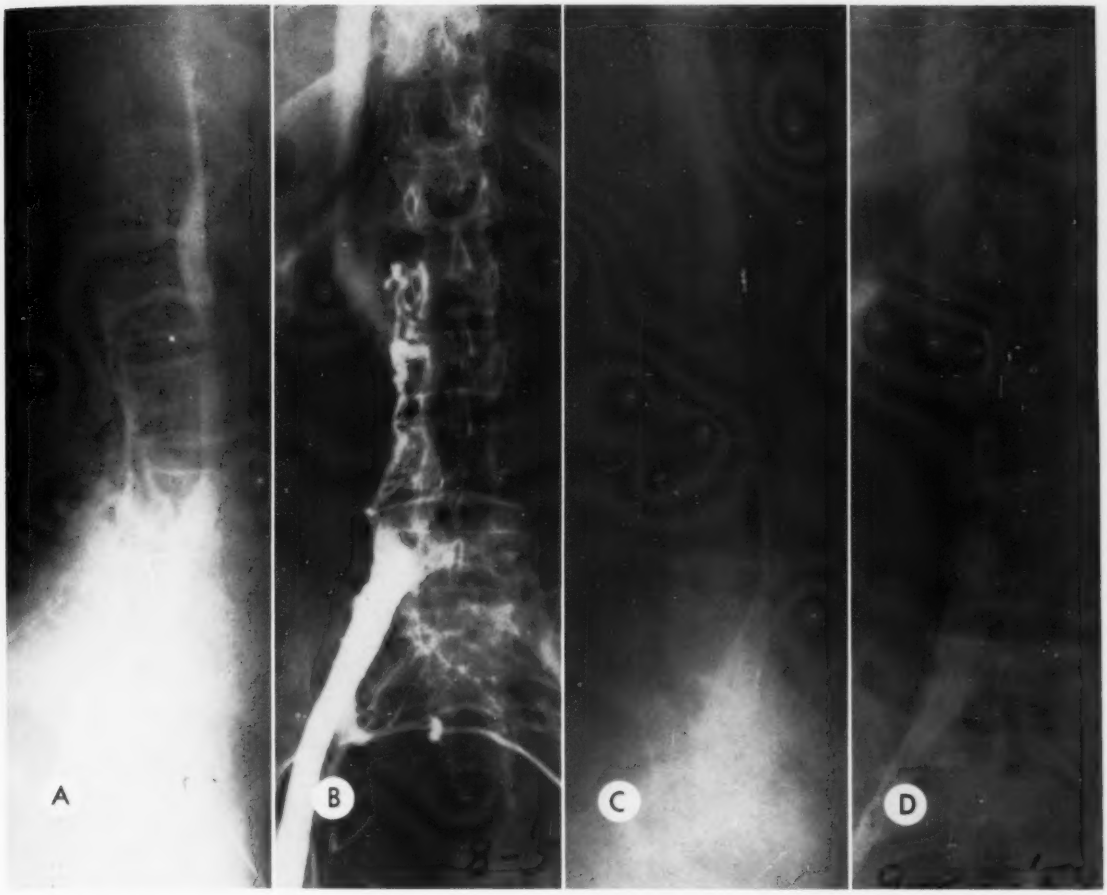

FIG. 8. This fifty-six year old white female received radiation therapy for giant follicular lymphoma of the cervical lymph nodes in 1953. Unexplained weight loss and flank pain were present on admission. Physical examination was negative. (*A* and *B*) Inferior vena cavagrams reveal a partial obstruction of the vena cava overlying L_4 with extensive collateral circulation and a second mass from D_{11} to L_2 elevating and displacing the vena cava. (*C* and *D*) Following a 3,000 r tumor dose to these retroperitoneal lymph nodes the inferior vena cava returned to normal except for slight elevation and displacement at the D_{12} to L_1 level. Note the absence of collateral circulation.

eral economy. In this case a less vigorous plan of therapy may be indicated. On the other hand, when the presence of localized disease is supported by negative vena cavagrams, more intensive radiation therapy is then indicated.

In occult malignancies special studies often fail to reveal the suspected neoplasm. Figure 5, *A* and *B*, illustrates a case of Hodgkin's disease which was undiagnosed for fifteen months, during which time the patient was hospitalized on two separate occasions. Special studies including bone marrow examinations were repeatedly negative. When a lymph node in the axilla became enlarged and was biopsied, the diagnosis of Hodgkin's disease was made. An inferior vena cavagram at that time revealed extensive retroperitoneal involvement which was undoubtedly the cause of intermittent fever and malaise. Had an inferior vena cavagram been done as an integral part of the routine work-up of occult malignancy the diagnosis could have been made several months sooner. After the presence of a retroperitoneal neoplasm is established, serial vena cavagrams provide objective evidence of the response to therapy. Figure 6, *A–D*, illustrates a case in which extensive retroperitoneal lymph-

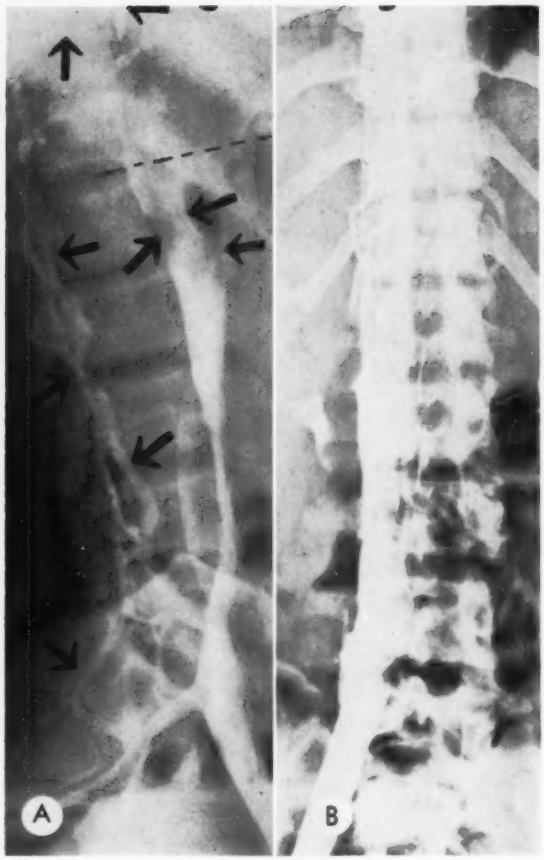

FIG. 9. This twenty-six year old white male was admitted with nausea, vomiting, and progressive pain in the lumbar region for the preceding month. Intravenous pyelography, upper gastrointestinal series and barium enema examination were normal. (*A* and *B*) Inferior vena cavagrams demonstrate numerous masses compressing the vena cava in the lower lumbar region and completely obstructing the flow of contrast material at L1. Note the large collaterals with the contrast material again entering the vena cava at D11-D12, which is above the complete block. One week later the patient became comatose and expired. Autopsy revealed anaplastic metastatic carcinoma in the brain and the same cell type in the retroperitoneal lymph nodes. The primary site could not be determined. Of interest is the demonstration by vena cavagraphy of the extensive collateral circulation as a possible route for the cerebral metastases.

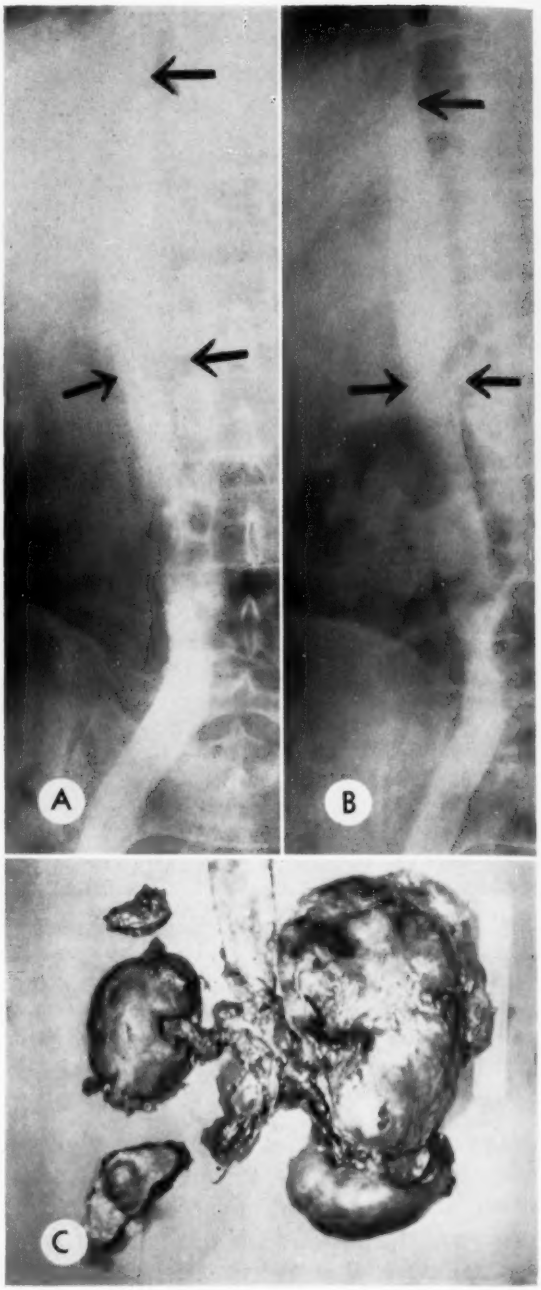

FIG. 10. A thirty-five year old white male was admitted with a large left abdominal mass which displaced and distorted the collecting system of the left kidney. (*A*) The inferior vena cavagram demonstrates a mass of lymph nodes surrounding the vena cava at the L2-L3 level and a suggestive mass at D11. Needle biopsy revealed a carcinoma of the adrenal cortex. Because of the metastatic spread disclosed by the inferior vena cavagram,

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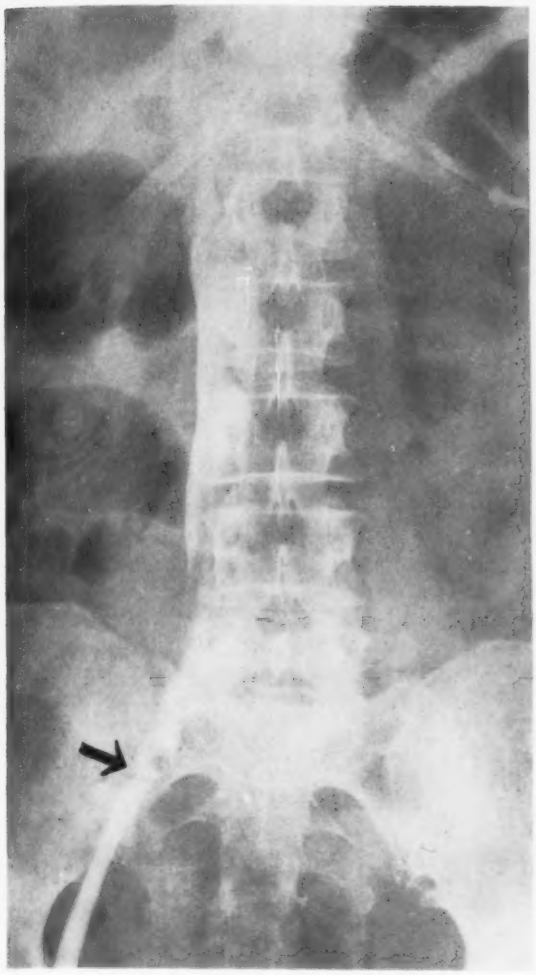

Fig. 11. An inferior vena cavagram demonstrates metastatic right common iliac lymph nodes in a patient with carcinoma of the cervix. Note the filling defect laterally, at a site where there are no tributaries to this vein. Surgery confirmed the roentgenographic findings.

radiation therapy was given to the left flank and to the metastatic L_2-L_3 region. (*B*) One week after completion of therapy, the inferior vena cavagram shows considerable improvement at the L_2-L_3 treatment site, but the suspicious D_{11} area is grossly abnormal. At this time small metastatic nodules began to appear in the lungs. (*C*) At autopsy the diagnosis was confirmed and the metastatic masses at L_2 and D_{11} were found to be separate from the primary adrenal tumor. Note the enormous size of the left adrenal gland as compared to the right adrenal gland and kidneys.

Fig. 12. A forty-three year old white female was admitted with abdominal distention. Pelvic examination revealed a mass in the pelvis. (*A* and *B*) Inferior vena cavagrams reveal a second mass at the L_1-L_2 level. Note the pressure defects on the anterior surface of the vena cava rather suggesting an abdominal origin. Surgery revealed a carcinoma of the ovary with peritoneal implants and a fixed mass in the region of the celiac axis.

adenopathy was not apparent at exploratory laparotomy because of the massive mesenteric lymph nodes. Biopsy of the mesenteric lymph nodes revealed giant follicular lymphoma. A postoperative inferior vena cavagram revealed marked elevation caused by retroperitoneal lymphadenopathy. Serial inferior vena cavagrams demonstrated the response to therapy (Fig. 6, *C* and *D*).

Partial or complete obstruction of either of the venae cavae can be readily diagnosed and the exact site determined only by vena cavagraphy (Fig. 7–14). This is of primary value in inferior vena caval obstruction, in which clinical symptoms are absent in 50 per cent of cases.[4] Intensive local radiation therapy to these sites may prevent or alleviate distressing obstructive symptoms. Illustrative cases are presented in Figures 7–12.

Although routine methods are usually adequate in evaluating pelvic pathology, the anterolateral areas of the pelvis are

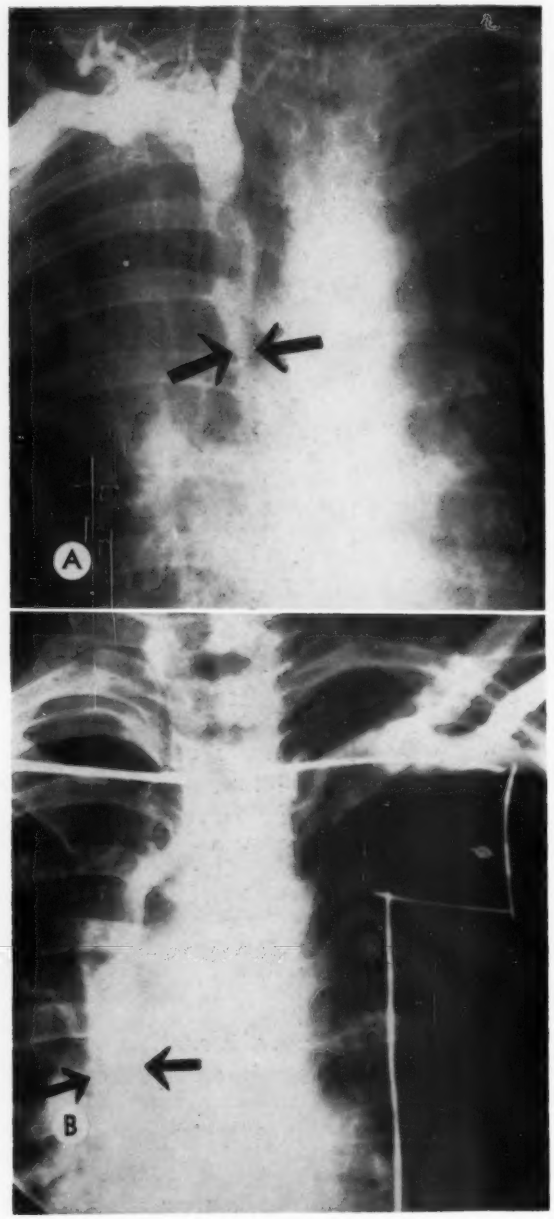

FIG. 13. This fifty year old white female was admitted because of a mass seen on a routine chest roentgenogram five years following a left radical mastectomy for carcinoma. Biopsies of the scalene lymph nodes were negative and open thoracotomy was scheduled. During the induction of anesthesia the patient suddenly developed a superior vena caval obstruction with marked cardiovascular changes. (*A*) A superior vena cavagram taken the following day revealed the almost complete obstruction. Had the study been performed before the anesthesia the near fatal reaction could have been prevented. (*B*) A superior vena cavagram taken after three weeks of radiation therapy demonstrates the normal width of the vena cava. Biopsy of the mass was performed without difficulty under general anesthesia. Microscopic sections revealed carcinoma compatible with breast carcinoma.

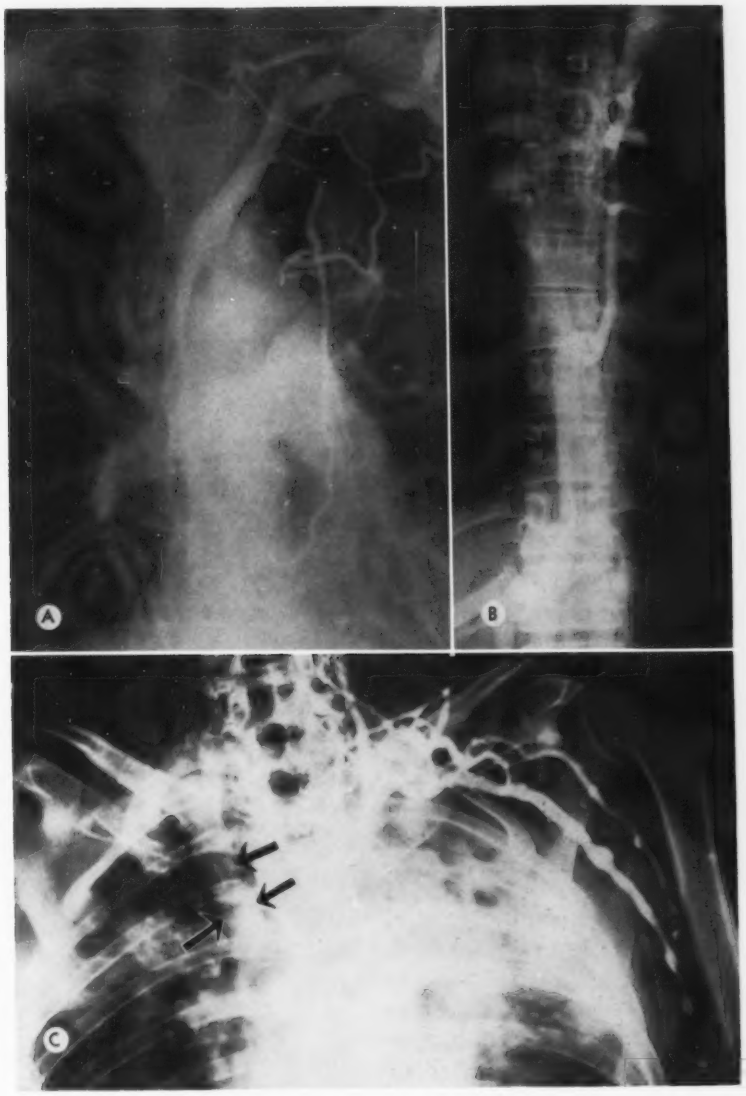

FIG. 14. The mediastinal venous collateral circulation which is visualized varies with the site of the obstruction. (*A*) With incomplete low superior vena caval obstruction the internal mammary veins are well visualized. (*B*) Complete obstruction of the superior vena cava results in visualization of the hemiazygos and azygos systems. (*C*) Complete obstruction of one innominate vein causes the contrast material to reflux through innumerable cervical veins to the contralateral innominate vein.

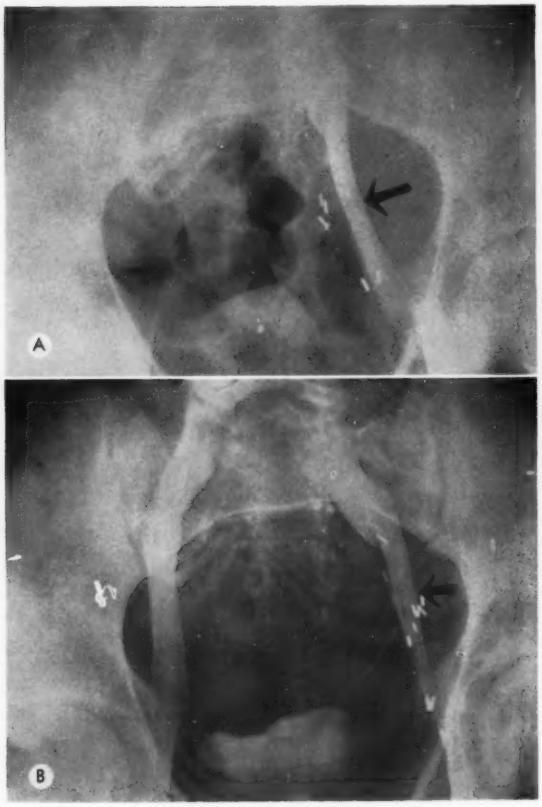

FIG. 15. A palpable mass in the left iliac fossa was biopsied revealing a reticulum cell sarcoma. Before radiation therapy a left femoral injection (*A*) outlines the medial confines of the tumor and provides a basis for evaluating the radiation response. After a 3,500 r tumor dose in three weeks, a repeat injection (*B*) reveals the minimal deformity of the common iliac vein; this has remained unchanged over the past year. A sensitive objective method for detecting possible early recurrence is provided.

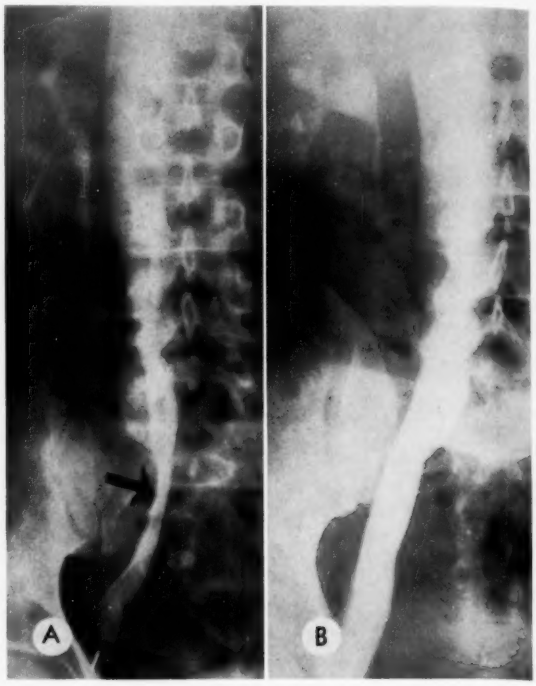

FIG. 16. An obese white male, thirty-eight years of age, was clinically suspected of having a malignant process, but physical examination and routine roentgenographic and laboratory findings were negative. (*A*) An inferior vena cavagram reveals a large mass of iliac lymph nodes (arrow). Compare with *B*, a normal inferior vena cavagram. Biopsy revealed Hodgkin's disease. Following a 3,500 r tumor dose in three weeks to the right lower quadrant, a repeat inferior vena cavagram was negative and has remained so at three, six, and twelve month intervals.

better studied by iliac venography. Examples of pathology demonstrated by contrast visualization of these tributaries of the inferior vena cava are illustrated in Figures 15, *A* and *B;* 16, *A* and *B;* and 17, *A* and *B*.

The inferior vena cava is intimately related to the right adrenal gland, right kidney, liver, and head of the pancreas. Therefore, pathologic enlargement of these structures can be detected by inferior vena cavagraphy.

SUMMARY

Over 300 vena cavagrams have been employed in the evaluation and management of patients with various malignancies in the past four years at the U. S. Naval Hospitals, Pensacola, Florida, and St. Albans, New Yark. The technique of both superior and inferior vena cavagraphy has been briefly described. Anatomic relationships of the venae cavae have been discussed and illustrative cases of a variety of tumors presented. These studies have been of particular value in cases of lymphoma, and genitourinary and mediastinal tumors.

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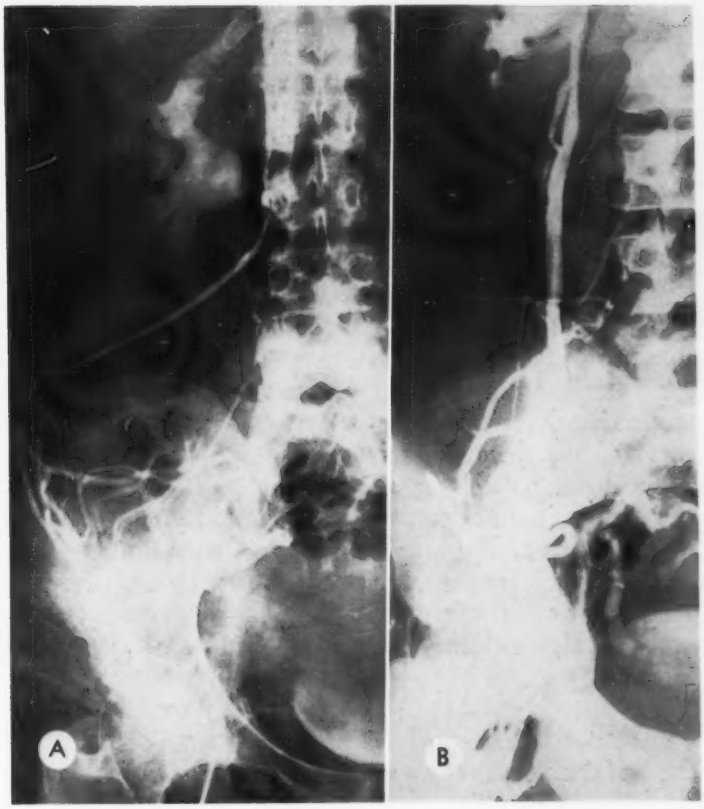

FIG. 17. External iliac vein obstruction may produce drainage into (*A*) the iliolumbar, ascending lumbar, and azygos systems or (*B*) into the spermatic vein.

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SIMPLIFIED TECHNIQUES IN THE EMPLOYMENT OF A ROTATIONAL COBALT 60 BEAM THERAPY UNIT*

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IF RADICAL treatment of small localized lesions by radiation therapy is to be successful, three basic requirements must be met. The first is an accurate knowledge of the location and extent of the volume to be treated. Secondly, a method must be devised which will permit the attainment of a satisfactory dose distribution which completely encloses this volume. Finally, this method must be employed to deliver an adequate cancerocidal dose in an optimum time to the volume in question. This paper deals with the second of these three requirements; *i.e.*, the attainment of an adequate dose distribution completely enclosing the tumor volume.

METHOD

The classic method of dose estimation as used in orthovoltage therapy (which shall be referred to here as "the per cent depth dose method") can be employed in cobalt 60 teletherapy with certain reasonable modifications. While in orthovoltage therapy the dose maximum is at the skin surface, in cobalt 60 teletherapy the maximum absorbed dose is at a depth of a few millimeters beneath the skin.[2,6] In the per cent depth dose method, the point on the central axis of the beam where the maximum dose is attained within the patient is used as a reference, and doses elsewhere are quoted as a percentage of the dose at this point. When this method is used in cobalt 60 teletherapy, the exposure dose rate is measured at a point in air which would correspond to a position 0.5 cm. beneath the presenting skin of the patient. Because of scatter from the diaphragm system, this exposure dose rate will be a function of the beam cross section. When the patient is placed in the beam, the absorbed dose rate at this point is given by the product of the exposure dose rate, the appropriate backscatter factor (which also depends upon the field area), and a factor[10] which serves to convert the exposure dose rate in roentgens per minute at this point to the absorbed dose rate in rads per minute. The absorbed dose rate at other points in the body is then found from the appropriate isodose distribution as a percentage of the maximum dose rate. In multiple field treatments, the dose at these points is merely the sum of the dose contributions from all the fields, and the over-all distribution within the patient is determined by summing the individual isodose distributions, which have been appropriately weighted for given dose.

This system of dosage estimation recommends itself for its simplicity, and it has stood the test of time in fixed field therapy. In rotation therapy, however, where the center of the tumor rather than the skin is placed at a fixed distance from the radiation source, the method becomes somewhat cumbersome. This is because the shape and nature of the isodose distribution are dependent on the source-to-skin distance, and in rotational or arc therapy this distance is continuously varying because of the anatomic contour. The method of "tumor-air ratios"[7,8] was developed to overcome this difficulty. In this *rotational* dosage system the exposure dose rate in air at the center of rotation as a function of beam cross section is first determined. The center of the volume to be treated is then placed at this point and the thickness of overlying tissue between the center and the skin surface is determined for an appropriate number of radii. Tumor-air ratio tables,[7,8,11] which express the ratio of absorbed dose in tissue to exposure dose in air as a function

* From The Ontario Cancer Foundation London Clinic, Victoria Hospital, London, Canada.

of depth of overlying tissue and field cross section, are then employed to determine the dose rate at the tumor when the beam axis is directed along each individual radius. If the rate of rotation is constant, the dose rates so determined can be averaged to give the effective dose rate during a cycle of arc or of full rotation.

The same principle can be used to advantage in stationary beam therapy. Figure 1 illustrates the method. The exposure dose rate in air at the center of rotation T is first determined as a function of beam cross section in the plane of T. When the patient is placed in the beam, the depth d of overlying tissue is determined either by a measurement on a body cross section or by the use of a calibrated front pointer attached to the head of the unit. The absorbed dose rate at T is then found by multiplying the known exposure dose rate by the appropriate tumor-air ratio as determined from the tables. The absorbed *dose* at T is given by the absorbed dose rate multiplied by the time of exposure. The absorbed dose at other points (*e.g.*, X) is then found by reference to the appropriate isodose distribution which is normalized to give 100 per cent[1,3,11] at the center of rotation T. The dose at T and X in multiple field distributions is then determined by summing the appropriate dose contributions from each field individually, and the over-all distribution is determined by the usual point-to-point method.

A number of advantages over more conventional methods become apparent when this approach is used with rotational types

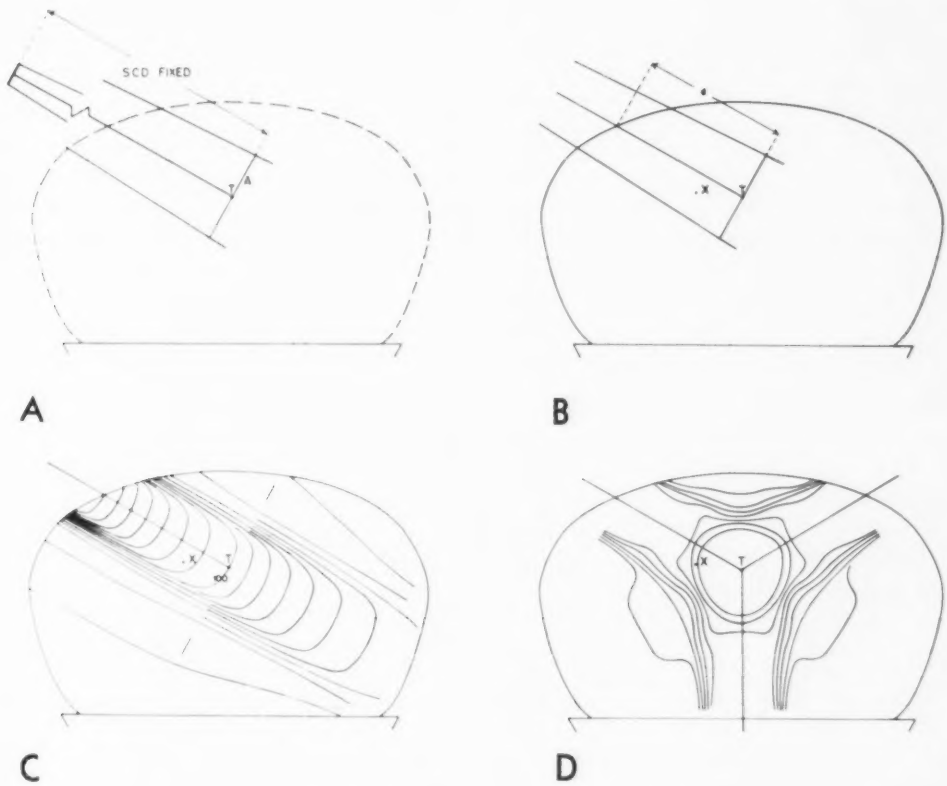

Fig. 1. Steps in dose estimation in fixed field therapy using the "tumor-air ratio" method. (*A*) Exposure dose rate at the center of rotation T is a function $E_T(A)$ of the area A of the beam in the plane of T. (*B*) Absorbed dose rate at T is $R_T(A, d) = E_T(A) \cdot T(A, d)$, where $T(A, d)$ is the appropriate tumor-air ratio. Absorbed dose at T is $D_T = R_T \cdot t$, where t is the time of exposure. (*C*) Absorbed dose at X is $D_x = D_T \cdot P$, where $P =$ (dose at X)/(dose at T). (*D*) Multiple field dose at T is $D_T = \sum_i D_{T_i}$ and at X is $D_x = \sum_i (D_{T_i} \cdot P_i)$.

of cobalt units. The first and most obvious advantage is that only one setting-up procedure is required, regardless of how many fields are to be used. This is because, with the patient placed so that the center of the treated volume is at the center of rotation, it is only necessary to rotate the unit from one entrance position to the next. On some types of rotational units this can be done from outside the treatment room. When the per cent depth dose method is used with this type of unit, each individual field must be set-up separately, with a consequent sacrifice of accuracy and time. Another advantage is that this approach focuses attention on the tumor volume to be treated, *i.e.*, the prescription of dose is to the tumor directly. The beam dimensions are chosen to enclose the tumor without reference to the area of the skin treated. While the dose delivered to the skin is readily calculable, it does not enter into the dosage prescription in the first instance. As has been pointed out, the method can be used with equal facility for fixed beam and arc therapy, and radically simplifies the determination of complete dose distributions, particularly in the use of wedge fields.

Du Sault[3] has discussed applications of this method in which a single isodose distribution[1] is used, regardless of the depth overlying the tumor center, on the assumption that the center lies in the region where the central axis depth dose curve is exponential. Corrections must be applied in the determination of the dose at points between the center and the skin, especially in the case of head and neck lesions where the skin-center distance is small.

The necessity for such corrections is eliminated if for each field size there is available a number of isodose distributions, each applicable to a range of skin-center distances. A satisfactory degree of accuracy can be attained by the use of three such distributions, measured with thicknesses overlying the center of 5, 10 and 15 cm. (Fig. 2). When the depth encountered clinically differs from these values, the isodose distribution for the nearest measured depth is employed. As seen in Figure 2, the error introduced by this approximation in the immediate region of the tumor is at most 2 per cent. Since the dose rate is determined accurately at the center of rotation by a method which is quite independent of

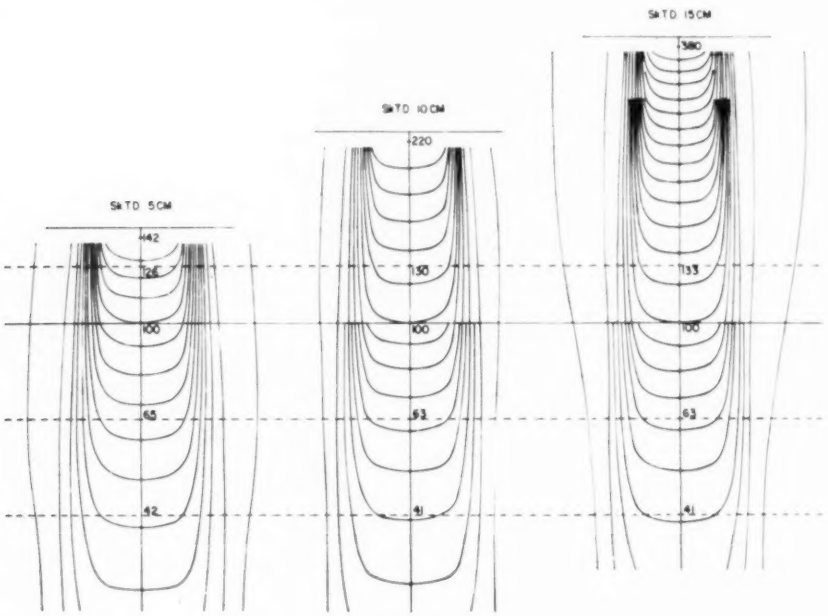

FIG. 2. Comparison of isodose distributions for a field of dimensions 6 cm. by 8 cm. at the center of rotation, with skin-tumor distance of 5, 10 and 15 cm. The distributions are normalized to 100 per cent at the center of rotation.

the isodose distribution, any error involved is a minimum in the volume of interest.

This fact is significant in that it makes possible the production of multiple field distributions without reference to any particular anatomic contour. That is, one can, at leisure, combine any number of fields directed at the center of rotation from different angles and so produce standard dose distributions of general usefulness. When such a standard distribution is applied to the contour of a particular patient, it will indicate with a high degree of accuracy the dose at points in the immediate vicinity of the tumor volume, and with somewhat less accuracy the dose at points remote from the center of the tumor. The inaccuracy over the whole of the range from the center of rotation out to the skin need not exceed 5 per cent under normal circumstances. Thus it is possible to build up a library of standard dose distributions which can be applied as required to dose computations involved in treatment. Such a library should contain dose distributions for multiple open fields, multiple wedge fields and moving beam therapy. Examples of such distributions are shown in Figures 3, 4, 5 and 6. Rotational and arc distributions can be calculated by the method of Gregory.[4]

The method is, then, to obtain an anatomic contour of the patient in the plane of treatment, to draw onto the anatomic contour the outlines of the tumor as established by roentgenographic or other methods, and then to choose the dose distribution from the ones available which will best enclose the tumor volume as drawn. An example is shown in Figure 7.

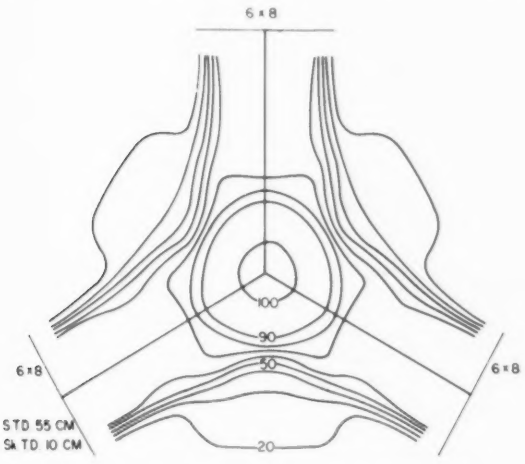

Fig. 3. Dose distribution for three 6×8 cm. fields at 120 degrees to one another. Source-tumor distance 55 cm.; skin-tumor distance 10 cm.

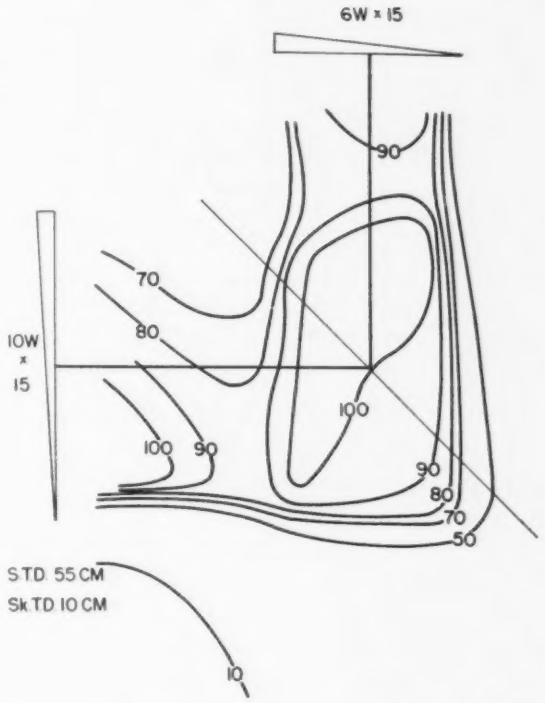

Fig. 4. Dose distribution for two wedge fields at 90 degrees. Left wedge 10 cm. wide; top wedge 6 cm. wide.

It is seen that the center of rotation need not necessarily coincide with the geometric center of the tumor, and that the contribution to the central dose need not be the same for all fields. From such a superposition it is possible to obtain the points on the skin at which the central axes of the individual beams are incident, together with their relative directions. The depths d_1, d_2, and d_3 from the skin to the tumor on the central axes can either be measured on the contour as shown, or, when the patient is first set-up for treatment, they can be measured with a calibrated front pointer attached to the unit.

When one or more of the incident beams impinges upon the skin at other than normal incidence, it may be argued[5] that corrections must be made to the resulting

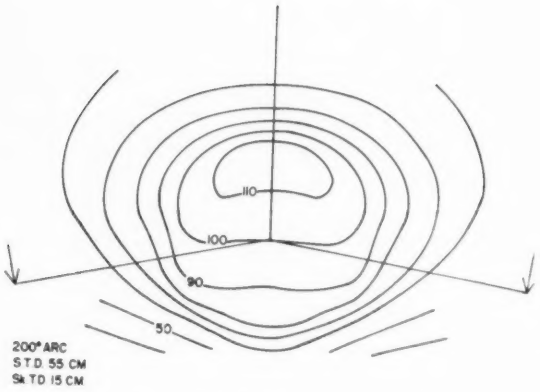

FIG. 5. Dose distribution for a 200 degree arc. Field size 10×12 cm.

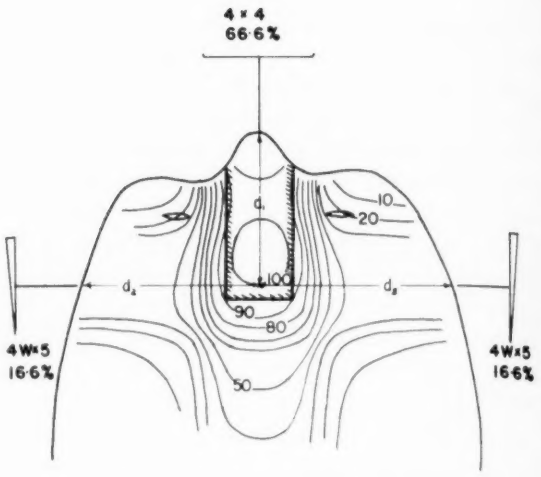

FIG. 7. Superposition of a standard dose distribution on a body cross section including the ethmoid sinuses. The 90 per cent dose contour encloses the treated volume.

isodose distribution to take into account the differential absorption on the two sides of the treatment field. An investigation into the alteration in the standard isodose patterns has shown that, while the patterns are undoubtedly modified somewhat due to this effect, the distortion of a multiple field isodose distribution is relatively minor provided the incident angles are not too extreme. This is illustrated in Figure 8 for the case of two wedge fields at right angles. In a similar way there will be a small amount of distortion in rotational and arc distributions due to the same effect. Again these distortions are relatively minor and have a negligible effect when the dose distribution is applied to the treatment of a particular patient.

The standard dose distributions are valid only in the plane of treatment, *i.e.*, in the plane containing the central axes of the individual beams. It is important to know the separation of the significant isodose surface in a direction perpendicular to this plane as a function of the field dimensions in this direction. Curves of the type shown in Figure 9 are useful in choosing the field dimensions which will be required to enclose the tumor.

It will be observed that, in the dose distributions of Figures 3, 4 and 6, the 100 per cent dose contour encompasses a very small volume whose shape is not necessarily

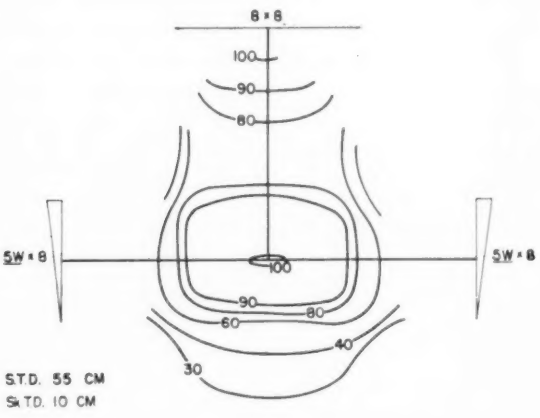

FIG. 6. Dose distribution for the combination of a single 8×8 cm. open field with two 5×8 cm. wedge fields.

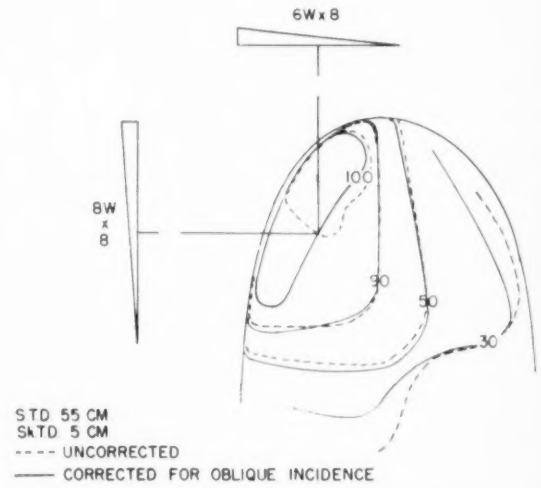

FIG. 8. A comparison of dose distributions for two wedge fields at 90 degrees, with and without correction for oblique incidence.

characteristic of the dose distribution as a whole. It is apparent that the 90 per cent contour approximates the nominal dimensions of the incident beams, and so field dimensions should be chosen which produce a distribution enclosing the known tumor volume within the 90 per cent contour. This choice implies the acceptance of a maximum dose within the tumor volume which is at least 11 per cent higher than that obtaining on the periphery of the tumor. This inhomogeneity within the tumor volume is, of course, characteristic of all such distributions regardless of the method of treatment and calculation used.

In practice, it is first necessary to know the desired position of the center of rotation with reference to skin marks on the exterior of the patient. The minimum number of such skin marks that will uniquely define such a point is three, and these marks should lie in a cross sectional plane through the center of the tumor. Figure 10 shows their relative relationship to one another and to the tumor center *T*. The line *BTD* passes through the center of the tumor and the line *AT* intersects it at right

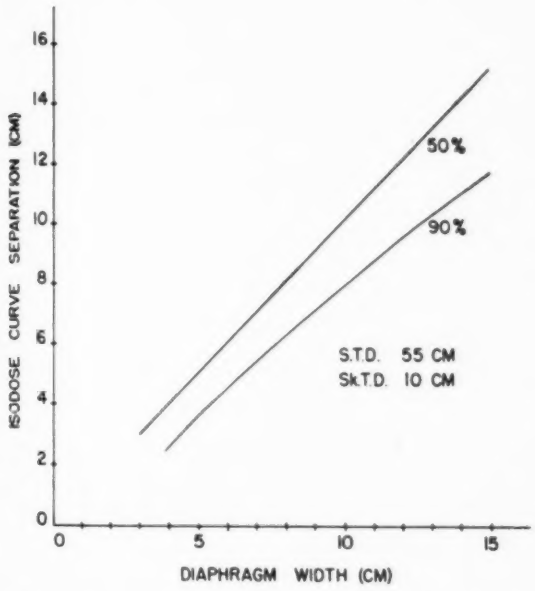

Fig. 9. Graph showing, as a function of diaphragm setting, the separation of the 90 and 50 per cent isodose surfaces at the center of rotation in a direction perpendicular to the plane of treatment. Theratron junior cobalt 60 unit; 1.5 cm. diameter source; source-center distance 55 cm.

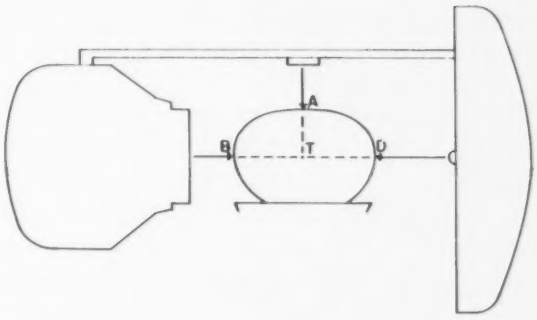

Fig. 10. Diagram illustrating the use of three light beams from the unit to place the point *T* at the center of rotation.

angles at the center. In order to use this method, it is necessary to have three directions defined from the unit itself. One of these directions may be defined by using the projection of the cross hairs in the light beam from the head of the unit. A back pointer light which directs a beam backward along the central axis in a direction toward the source defines the second of these directions, and a third light beam can be projected from a mounting similar to that shown in the figure in a direction at right angles to the line defined by the first two and intersecting this line at the center of rotation. Alternatively, since the center of rotation is a point fixed with reference to the walls of the treatment room, light beams can be projected from the walls and ceiling to meet at this point. With the patient supine or prone on the treatment stretcher, it is possible to position him in such a way that the three light beams impinge on the skin over the three skin marks. Since the beams intersect at the center of rotation, this procedure ensures that the appropriate point in the tumor is properly placed. The unit is then rotated to the desired treatment angle and the depth of tissue overlying the center of rotation along the central axis of the treatment beam is then measured, using a calibrated front pointer attached to the head of the unit. This depth is used to derive the dose rate at *T* for the appropriate field size by the use of tumor-air ratio tables.

In order to determine the absorbed dose rate at the center of rotation for a particular field, one must know the variation of

exposure dose rate with field size at the center of rotation and have available a table of tumor-air ratios appropriate to the particular treatment unit. It is possible to combine these data in the form of a single calculator.[9] In such a calculator the product of exposure dose rate variation at the center of rotation and the tumor-air ratio are plotted on full logarithmic paper as a function of field area, with depth of overlying tissue as parameter. The principle of the slide rule is used to calculate the treatment time for any particular tumor dose required.

SUMMARY

In summary, this paper describes a simplified method of tumor dose computation and isodose charting which is applicable to therapy units in which the radiation source is constrained to move in a circle with the central axis of the beam pointing at a fixed point in space. The method of tumor-air ratios is employed to determine the dose rate at a point in the volume to be treated, in both moving field and stationary field techniques. Isodose charts which are normalized to 100 per cent at the center of rotation are then employed to determine the dose rate at other points within the treatment field. Using this method, it is possible to build up a library of standard dose distributions for stationary, wedge and rotational treatments which can be used directly to indicate the dose distributions within individual patients. It is seen that by the use of such standard distributions a large amount of very tedious computation is eliminated, and complete isodose charting for each patient treated can now become the rule rather than the exception. Since the errors involved in the use of these standard distributions are well within the uncertainties otherwise inherent in radiation therapy, the method permits of great simplification in treatment planning without a significant sacrifice in accuracy. The interchange of precalculated dose distributions between institutions employing the same type of unit becomes an attractive possibility.

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The methods described in this paper are the result of the joint efforts of the physics and radiotherapeutic staff of this Clinic. The library of standard distributions has been built up through the work of Mr. P. M. Pfalzner and Dr. H. I. S. Ferguson.

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Vol. 86, No. 4

THIMBLE CHAMBER CORRECTIONS BELOW 100 KV. EFFECTIVE

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IT IS well known that thimble ionization chambers will give erroneous results if used to measure roentgen-ray beams outside of the useful energy range designated by the manufacturers. Unfortunately, the meaning of the manufacturer's statement, "Good for energies from 30 to 400 kv. effective," is frequently misinterpreted by those using this instrument when measuring dosage in superficial therapy. It is the intention of this paper to draw attention to this common misinterpretation in order to: (1) stimulate interest, leading to further investigations by those laboratories adequately equipped to study this problem; (2) encourage the widespread dissemination of existing information on this problem; (3) elucidate the meaning of the manufacturer's claims; and (4) improve dosage specification in superficial therapy.

If a typical response curve for thimble ionization chambers as reported by the manufacturer is presented in terms of half value layer, as shown in Figure 1, the inadequacy of this equipment for the measurement of superficial therapy beams becomes obvious.

In addition to the data supplied by the manufacturers, some data are available in the literature.[1,2] The data of these authors have been rearranged and plotted along with those from two manufacturers and are shown in Figure 2. The method of converting these data can be deduced from the data presented in Table 1.

Although the curves of Figure 2 may not be applicable to any one r-meter, they may serve as a temporary guide for those who at present do not employ any correction factor in this range. Most superficial ther-

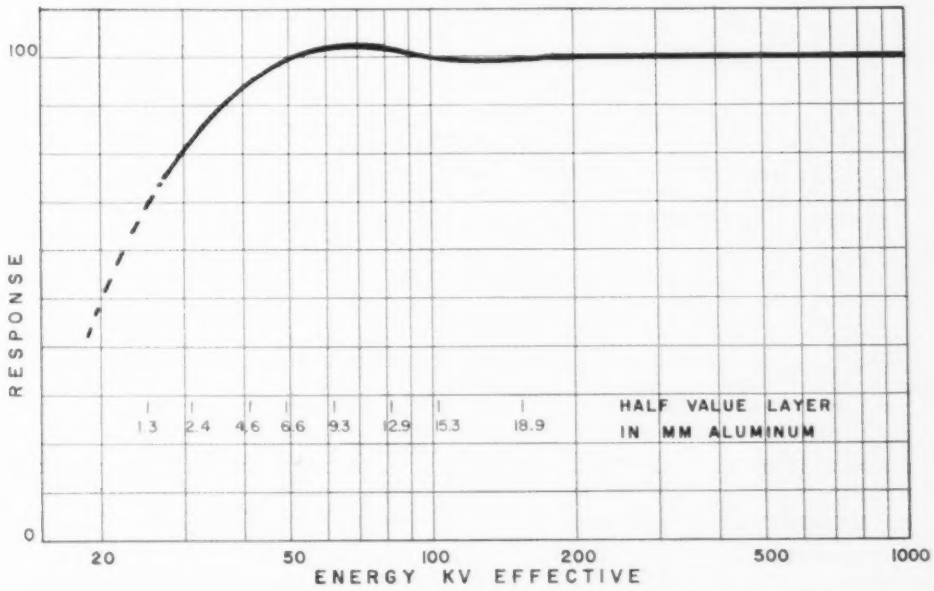

FIG. 1. Typical response curve of a Landsverk model L-64 r-meter as reported by the manufacturer. Half value layers have been calculated by the author. The manufacturer stresses that "special attention is given to calibrations in the energy ranges most commonly used in x-ray and radium therapy." Victoreen's typical response curve is similar. (Published with permission from the Landsverk Electrometer Company.)

TABLE I

CORRECTION FACTORS

kv. Effective	Effective Wavelength Angstroms	μ/ρ	Half Value Layer mm. Al	Correction Factors	
				Victoreen	Landsverk
82	0.15	.198	12.9	.99	.99
62	0.2	.274	9.3	.98	1.00
49	0.25	.388	6.6	.99	1.01
41	0.3	.557	4.6	1.00	1.06
31	0.4	1.09	2.4	1.02	1.22
25	0.5	1.95	1.3	1.05	1.43
21	0.6	3.22	0.8	1.08	—
15	0.8	7.32	0.35	1.22	—

The data of columns 1, 2, and 3 are obtained from Table 2.6 of Handbook of Radiology, R. H. Morgan and K. E. Corrigan. The Year Book Publishers, Inc., Chicago, 1955.

Column 4 was calculated on the basis of simple exponential absorption.

The values of column 6 were obtained from Landsverk's typical response curve which is shown in Figure 1. Victoreen's values were obtained from typical response curve for Model 70-5 Chamber, Victoreen Instrument Company, personal communication, August, 1960.

apy equipment comes within this scope, as is shown by the typical half value layers listed in Table II.

Those desiring more than a temporary guide constructed from data in the literature must have their equipment calibrated by the National Bureau of Standards where, according to Title 15, chapter 11, part 204 of the Federal Register, calibration at 4 half value layers in this range can be sup-

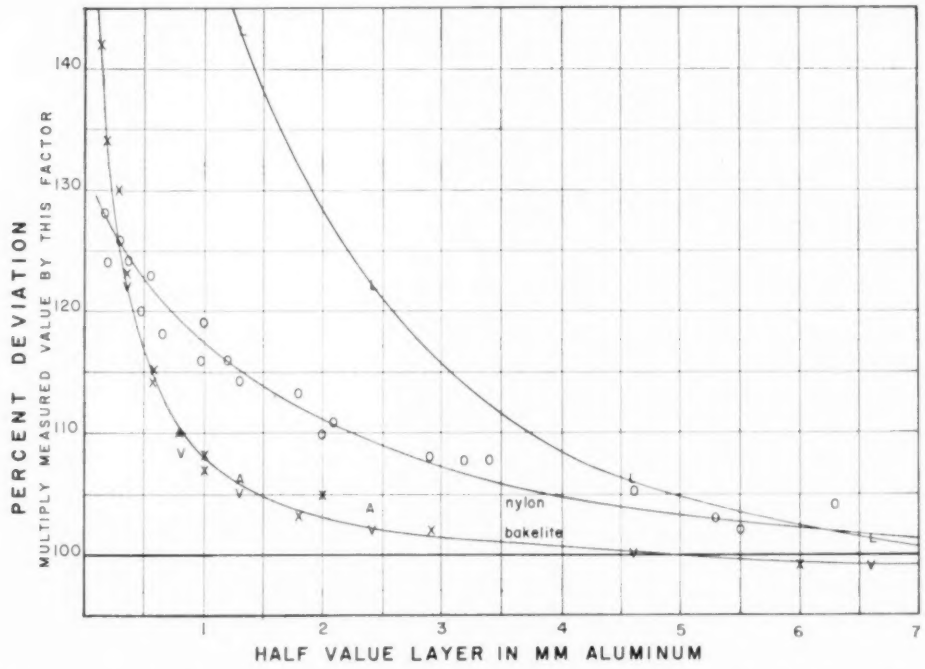

FIG. 2. R-meter correction factors for Victoreen nylon and bakelite probes and the Landsverk L-120 series probes. It is possible that the curves are more closely related to chamber size than composition. The plotted points were obtained from the following sources: X and O, Day;[1] A, Victoreen *et al.*;[2] L, Landsverk Electrometer Company brochure; V, Victoreen Instrument Company, personal communication, August, 1960.

TABLE II

TYPICAL HALF VALUE LAYERS FOR SUPERFICIAL ROENTGEN THERAPY EQUIPMENT

Manufacturer	kv.	Added Filter	HVL mm. Al
Picker	74	none	0.65
		1 mm. Al	1.3
	120	none	0.8
		1 mm. Al	2.0
		3 mm. Al	3.6
Keleket	60	none	0.85
	100	none	1.3
		2 mm. Al	3.4
General Electric (KX-10)	70	none	1.4
	100	none	1.8
	125	3 mm. Al	4.0

These data were obtained from calibration charts in our file.

plied for a 25 r chamber only. The individual user must then provide his own secondary calibration on other chambers.

SUMMARY

While this paper does not give new data on this problem, it does present existing data in a more utilitarian form and brings attention to the necessity of correcting r-chamber measurements in the calibration of output from superficial roentgen therapy apparatus. These corrections, when properly applied, should improve the specification of dosage.

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THE EFFECTS OF CARDIAC IRRADIATION UPON THE NORMAL CANINE HEART*

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CARDIAC irradiation has been proposed as a possible therapeutic method for inducing an increase in myocardial vascularity in coronary artery disease. In earlier publications[9,10,11] electrocardiographic and physiologic data obtained from a study of animals subjected to cardiac irradiation as well as an evaluation of the survival of such animals following acute coronary artery ligation have been presented. These studies have shown that the irradiated dogs withstand the acute myocardial insult of coronary ligation better than the nonirradiated control animals both in terms of survival and increased intercoronary anastomotic blood flow.

It is the purpose of this study to present a pathologic analysis of the effects of various dosages of radiation upon the canine heart and adjacent organs and tissues after varying periods of time. Dogs subjected to coronary artery ligation subsequent to irradiation as well as nonligated animals were studied.

METHOD

One hundred and fifteen mongrel dogs were used in this study. Thirty dogs received no irradiation and served as normal control animals. The remaining 85 animals were given varying doses of radiation and were studied at intervals of up to one year post irradiation (Table 1).

Cardiac irradiation was performed in the following manner. Of each dog a scout roentgenogram of the chest was taken to determine the heart location and size. This field was then mapped on the dog's thorax on both the left and right sides. The heart was irradiated by means of three treatments to the left chest field and two to the right chest field during a fourteen to seventeen day period. The treatments were given with a parallel opposing pair of fields ranging in size from 80–120 sq. cm. The average separation of the fields was 10 cm. Two hundred kilovolt roentgen rays which, after filtration, had a half value layer of 0.9 mm. of copper were utilized at a focal skin distance of 50 cm. The calculated dose to the heart in one group was 1,300 r (1,500 in air). Another group received a heart dose of 2,000 r (2,500 in air). A third group received a heart dose of 2,700 r (3,600 in air). This latter group received treatments in a manner similar to the other groups with the exception that three treatments were given to each chest field and the source of radiation was a cobalt 60 teletherapy unit.

Four to six days following the termination of the radiation treatments, one group of dogs was subjected to coronary artery ligation. Those dogs surviving this procedure were sacrificed two, four and six months post ligation for pathologic study. Those dogs which did not survive ligation or died within two months post ligation were also studied. The hearts were studied by injection of barium sulfate into the coronary orifices to outline the grossly functioning coronary circulation. Roentgenograms of the injected specimens were taken.[4] The hearts were then fixed in formalin and multiple transverse sections of the entire heart were made for gross and microscopic analysis. Some of the hearts were injected with vinylite plastic and corrosion prepara-

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This work has been supported in part by U.S.P.H.S. Grant H-3187.
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TABLE I

EXPERIMENTAL FACTORS IN CARDIAC IRRADIATION STUDY

Group	No. of Days	Estimated Dose to Myocardium (r)	Total Dose in Air (r)	Time of Pathologic Study
Control	30	0	0	Immediately—2 mo. post coronary artery ligation
Irradiated-ligated (coronary artery ligated 4–6 days post irradiation)	25	1,300	1,500	Immediately—6 mo. post coronary artery ligation
	25	2,000	2,500	Immediately—6 mo. post coronary artery ligation
Irradiated—ligated (coronary artery ligated 6 months post irradiation)	13	1,300 and 2,000	1,500 and 2,500	Immediately—2 mo. post coronary artery ligation
	3	2,700	3,600	Immediately—24 hr. post coronary artery ligation
Irradiated—nonligated	14	400–2,700	500–3,600	Several hours post first treatment—6 mo. post termination of radiation therapy
	5	2,100–2,700	2,700–3,600	One year post termination of radiation therapy

tions of the entire coronary circulation were made.[7] Sections of the sternum and rib cage were taken for bone marrow study. The lungs and mediastinal esophagus were also examined.

Another group of dogs, similarly irradiated, received no further treatment for a period of six months, after which it was subjected to coronary artery ligation. Similar studies were also performed on these animals. There was also a group of dogs (irradiated-nonligated) consisting of those animals which died of causes unrelated to the irradiation either during the course of irradiation or prior to the time of ligation. Postmortem and pathologic studies were performed on these animals.

In order to evaluate the possible late effects of irradiation, a group of 5 dogs was irradiated in a similar manner with dosages of 2,700–3,600 r in air (estimated 2,100–2,700 r to the myocardium). Prior to irradiation, weights, chest roentgenograms, electrocardiograms, hemoglobin, hematocrit, white blood cell counts and peripheral smears were obtained for use as baseline values. Nothing further was done for a period of one year. At the termination of this period, the dogs were again weighed and repeat roentgenograms, electrocardiograms and blood studies were performed. In addition, bone marrow from the iliac crest was examined in each dog. Following these studies the animals were sacrificed, and their organs examined grossly and microscopically.

RESULTS

A. BARIUM INJECTION STUDIES

Injection of the hearts of nonirradiated control dogs dying in the first twenty-four hours post ligation revealed the absence of barium in the anterior descending branch of the left coronary artery and its branches distal to the ligature applied at operation (Fig. 1*A*). The barium entered the right coronary and left circumflex coronary arteries and their branches, but did not

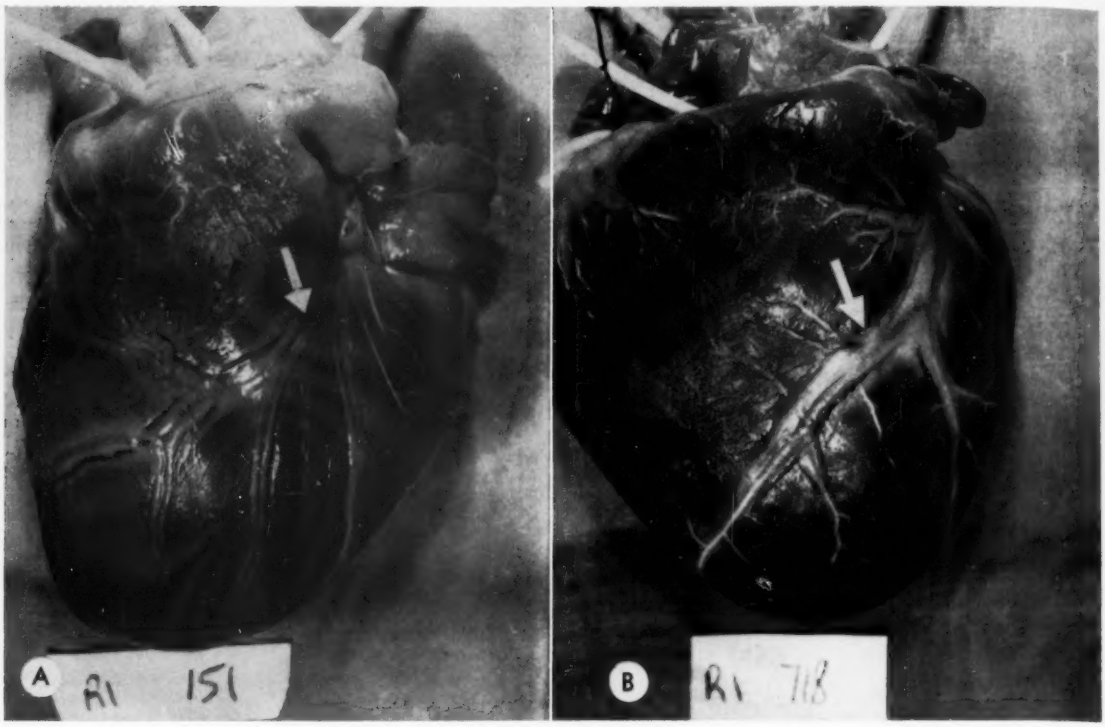

FIG. 1. (*A*) Anterior view of the heart of a nonirradiated dog dying one hour post ligation of the anterior descending coronary artery (arrow). Barium has been injected into the coronary orifices. Note the absence of barium in the ligated vessel and its branches. (*B*) Similarly injected heart of irradiated dog. Barium is seen in the anterior descending coronary artery and its branches.

anastomose with or enter the region of the heart supplied by the anterior descending coronary artery (Fig. 2*A*). Study of the irradiated hearts of similar dogs revealed a range of conditions varying from lack of filling of the anterior descending coronary artery to almost complete filling of the vessel (Fig. 1*B*) by retrograde flow of barium from branches of the left circumflex artery (Fig. 2, *B* and *C*). Control dogs dying twenty-nine hours and four days post ligation showed only slight to moderate retrograde filling of the anterior descending coronary artery and its branches; however, those control dogs surviving one to two months post ligation exhibited good filling of the ligated vessel. In comparison, the hearts of irradiated dogs dying four, ten and forty-two days post ligation revealed good to excellent filling of the anterior descending coronary artery up to the point of ligation by retrograde flow of barium through anastomotic connections between the ligated vessel branches and the adjacent intact coronary circulation. The hearts of irradiated dogs surviving two to six months exhibited excellent retrograde filling of the area of infarction and appeared more vascular than the normal heart.

B. ROENTGEN FINDINGS

Roentgenographic findings of the injected hearts corresponded to the gross observations mentioned above. In control dogs dying within twenty-four hours, a large avascular area was seen in the region of the distribution of the ligated coronary artery (Fig. 3*A*). This avascular area was not observed as frequently and did not appear as avascular on roentgenograms of comparable irradiated heart specimens (Fig. 3*B*). Roentgenograms of irradiated hearts two to six months post ligation demonstrated marked vascularity.

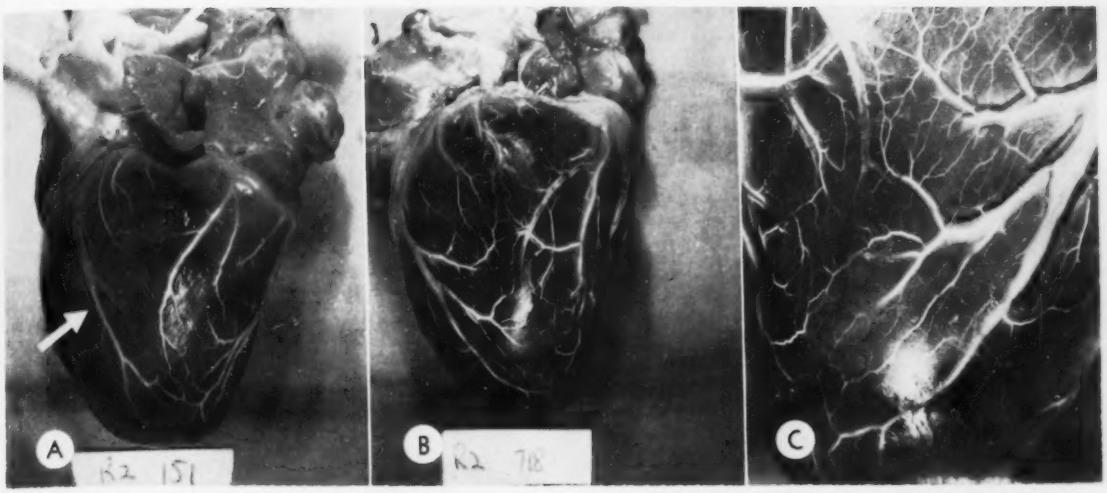

Fig. 2. (*A*) Lateral view of a barium injected nonirradiated heart. Arrow points to bare area (devoid of barium) corresponding to the distribution of the previously ligated anterior descending coronary artery. No significant intercoronary anastomoses are seen between the ligated vessel and the left circumflex artery which contains barium. (*B*) Similarly injected irradiated heart. Note the presence of numerous barium filled anastomotic connections between the anterior descending and left circumflex coronary arteries. (*C*) Close-up of area of intercoronary anastomoses seen in *B*.

C. Corrosion Preparation Studies

Corrosion preparations of hearts injected with vinylite demonstrated well the difference in vascularity between control and irradiated hearts. Figure 4*A* shows the vascular pattern of the normal heart. Figure 4*B* shows such a heart which has been subjected to ligation of the anterior descending coronary artery. This has created a large avascular area corresponding to the distribution of the ligated vessel. Figure 4*C* shows an irradiated heart one-half hour post ligation. This heart is similar to the normal nonligated heart in vascularity. An avascular area is not seen. The distribution of the anterior descending coronary artery has been completely filled by plastic material flowing through anastomotic channels from both right and left coronary artery branches.

D. Gross and Microscopic Studies—Pattern of Infarction

There was no distinct gross difference between the hearts of irradiated and control dogs in regard to the distribution of the infarcted area. In dogs surviving coronary artery ligation, the area of infarction usually involved most of the anterior wall of the left ventricle and the left border of the right ventricle. However, an analysis of the transverse sections of the hearts revealed an impressive contrast. All control animals presented infarcted cardiac muscle involving the entire thickness of the ventricular wall (Fig. 5 *A* and 6 *A*). Irradiated dogs of equal survival periods did not exhibit this "through and through" infarction of the ventricular wall, but instead had spared areas consisting of varying thicknesses of normal heart muscle in the subepicardium throughout the extent of the infarction (Fig. 5 *B* and 6*B*). There was no difference noted in the endocardial distribution of the infarction.

Microscopic sections taken from the region of infarction in the control hearts revealed complete necrosis of the ventricular wall (Fig. 7*A*). Sections of equivalent irradiated dogs' hearts exhibited necrosis plus a superficial area of normal muscle (Fig. 7*B*). Healing (fibroblastic proliferation) begins in this spared area of myocardium as early as four days post infarction while complete necrosis is still present in the center of the infarction. The sections

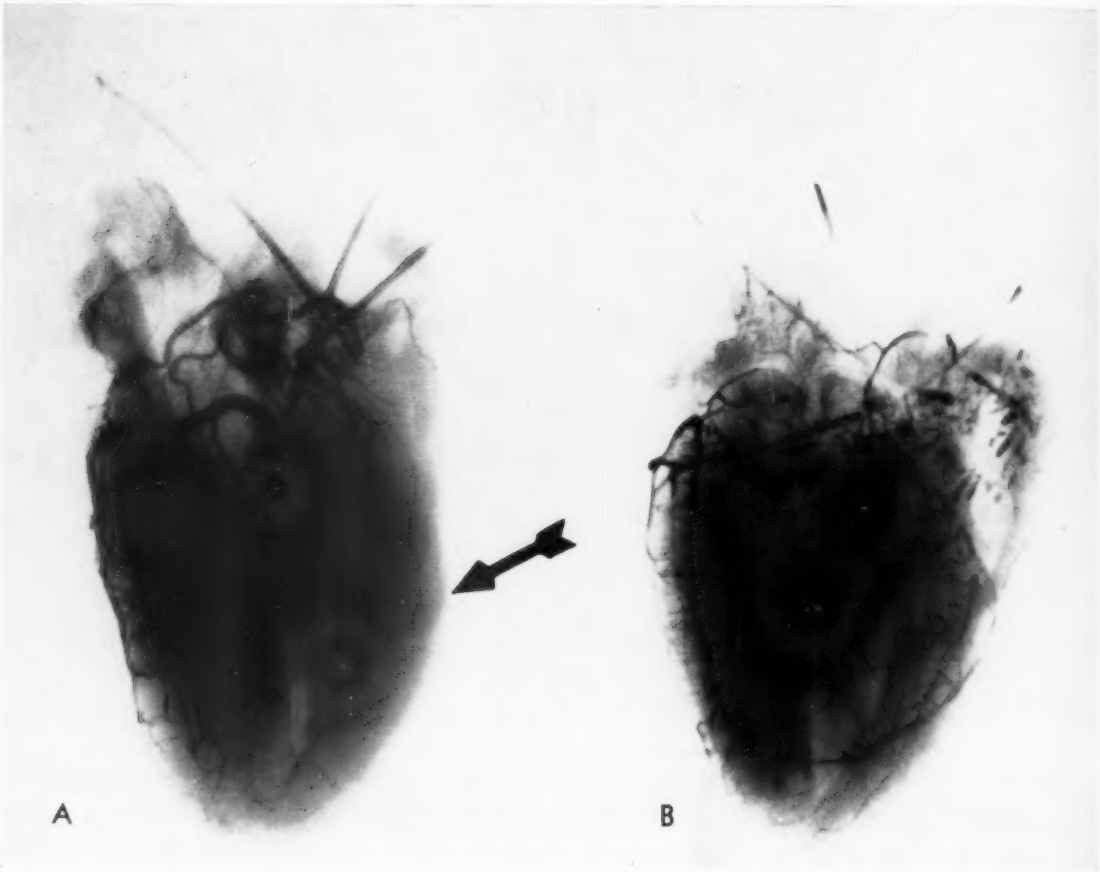

FIG. 3. (*A*) Roentgenogram of barium injected nonirradiated heart. Arrow indicates avascular area corresponding to the distribution of the previously ligated anterior descending coronary artery. (*B*) Roentgenogram of barium injected irradiated heart. The heart appears vascular. Note the absence of the avascular area seen in the region of the ligated vessel in the nonirradiated heart.

through the area of infarction in control dogs did not show this fibroblastic proliferation in the region of the subepicardium as there is no normal myocardial tissue from which this can occur. Only the viable tissue adjacent to the necrotic area of infarction exhibited fibroblastic proliferation in the control animals. A greater frequency of calcium deposition was seen in the area of infarction in the hearts of control animals one month or more following infarction.

E. RADIATION DAMAGE

There was no evidence of myocardial necrosis attributable to the effects of radiation in any of the irradiated hearts examined. An inflammatory response of pericarditis or myocarditis was not seen. There was no evidence of the formation of granulation tissue or myocardial fibrosis resulting from the cardiac irradiation. No evidence of obliteration of pulmonary or coronary vessels due to irradiation was seen on gross or microscopic analysis.

Examination of the lungs revealed the presence of a focal radiation induced pleuritis with subsequent pleural thickening in some of the irradiated animals. This effect was rarely seen in dogs receiving 1,500 r in air to the chest region. Those dogs receiving 2,500 r and 3,600 r to the chest region exhibited these findings fairly consistently six months post irradiation. These changes were not seen in the animals studied seven to twenty-four days following the termination of their treatments. The pleuritis in-

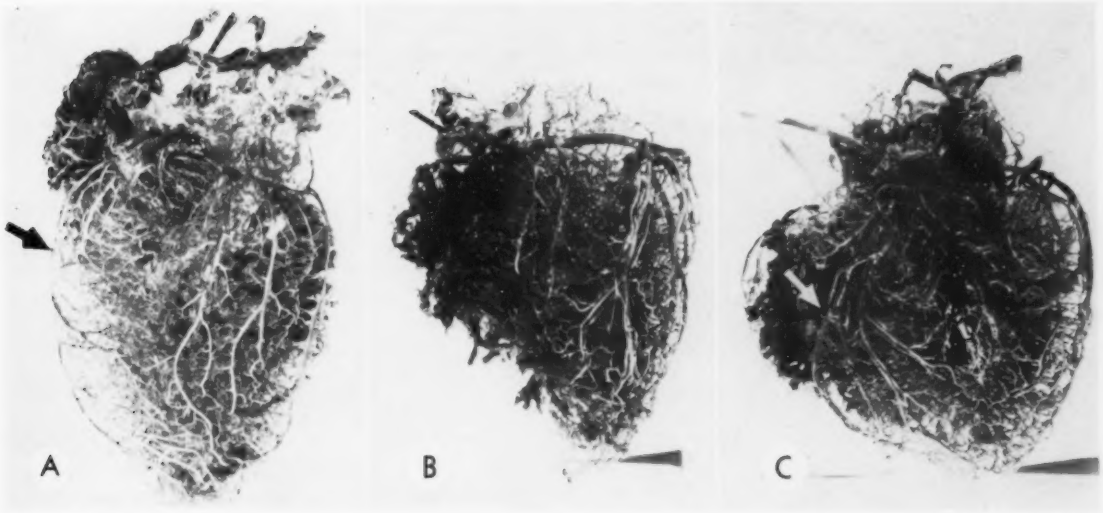

Fig. 4. (*A*) Vinylite injection and corrosion specimen of normal coronary circulation (lateral view). Arrow points to the anterior descending coronary artery. (*B*) Specimen of nonirradiated heart one-half hour post ligation of the anterior descending coronary artery. Note segment of absent coronary circulation which corresponds to distribution of the ligated vessel. (*C*) Specimen of irradiated heart one-half hour post ligation of the anterior descending coronary artery. The pattern of vascularity resembles a normal nonligated heart. Anterior descending coronary artery (arrow) has filled in a retrograde fashion by means of functioning intercoronary anastomotic channels.

volved only the area of lung underlying the field of irradiation and consisted grossly of patchy areas of grayish white pleural thickening (Fig. 8*A*). The lung tissue at a distance from the irradiated field appeared normal. Not all dogs receiving the same amount of irradiation showed the same degree of pleural involvement. Microscopic sections (Fig. 8*B*) revealed pleural fibrosis which in some cases involved several millimeters of the underlying lung parenchyma. The elastic membrane of the pleura was intact. There were no indications by physical or pathologic examination of any pulmonary effects of the radiation therapy sufficient to interfere with normal respiratory function. Examination of

Fig. 5. (*A*) Transverse section of nonirradiated heart two months post ligation of anterior descending coronary artery. Arrow indicates area of "through and through" infarction in the anterior wall of the left ventricle. (*B*) Comparable transverse section of irradiated heart (2,000 r). Arrow indicates area of spared normal muscle overlying area of infarction.

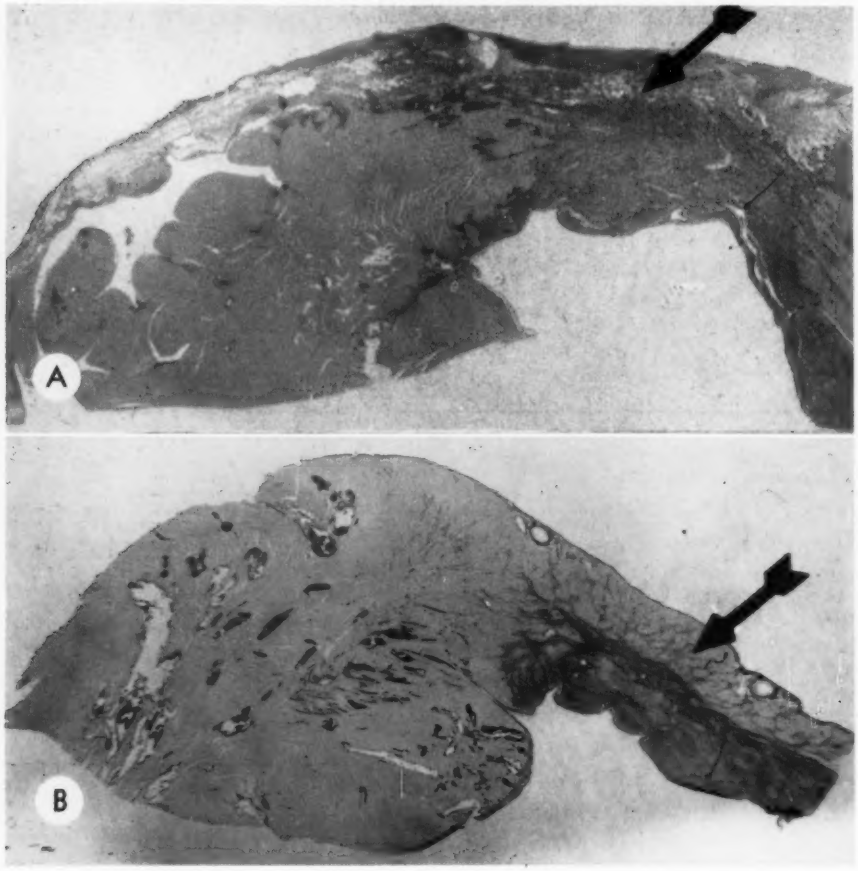

FIG. 6. (*A*) Van Gieson stained section through area of infarction in nonirradiated heart two months post ligation. Arrow indicates area of infarction extending from endocardial to epicardial surface. (*B*) Comparable section of area of infarction in an irradiated heart (2,000 r). Arrow points to normal muscle overlying the area of infarction. Note the presence of vessels in this area.

the lungs of nonirradiated dogs subjected to thoracotomy six months previously revealed, in many cases, pleural thickening of equal or greater severity than that seen in the irradiated animals. The pleural thickening did not, however, extend into the lung parenchyma in the nonirradiated animals.

Examination of the bone marrow taken from the ribs and sternum of irradiated animals revealed the following findings: Dogs receiving 1,500 r exhibited normal to moderate hypocellular marrow at six months post irradiation. Dogs receiving 2,500 r and 3,600 r exhibited moderate to marked focal hypocellular marrow changes six months post irradiation. In several dogs receiving 3,600 r, focal fibrosis was also noted. The most pronounced effects were seen in the direct field of irradiation (Fig. 9*A*). Sections taken from areas away from the irradiated field (Fig. 9*B*) showed normal hematopoiesis.

Other tissues in the irradiated dogs consisting of the mediastinal structures (trachea, esophagus, aorta) as well as stomach, small intestine, liver, spleen and kidney were examined. No changes in these were seen.

The results of studies performed one year post irradiation on those animals which received no surgery or other treatment were as follows:

1. All dogs maintained their pre-irradiation weight.

2. Chest roentgenograms and electro-

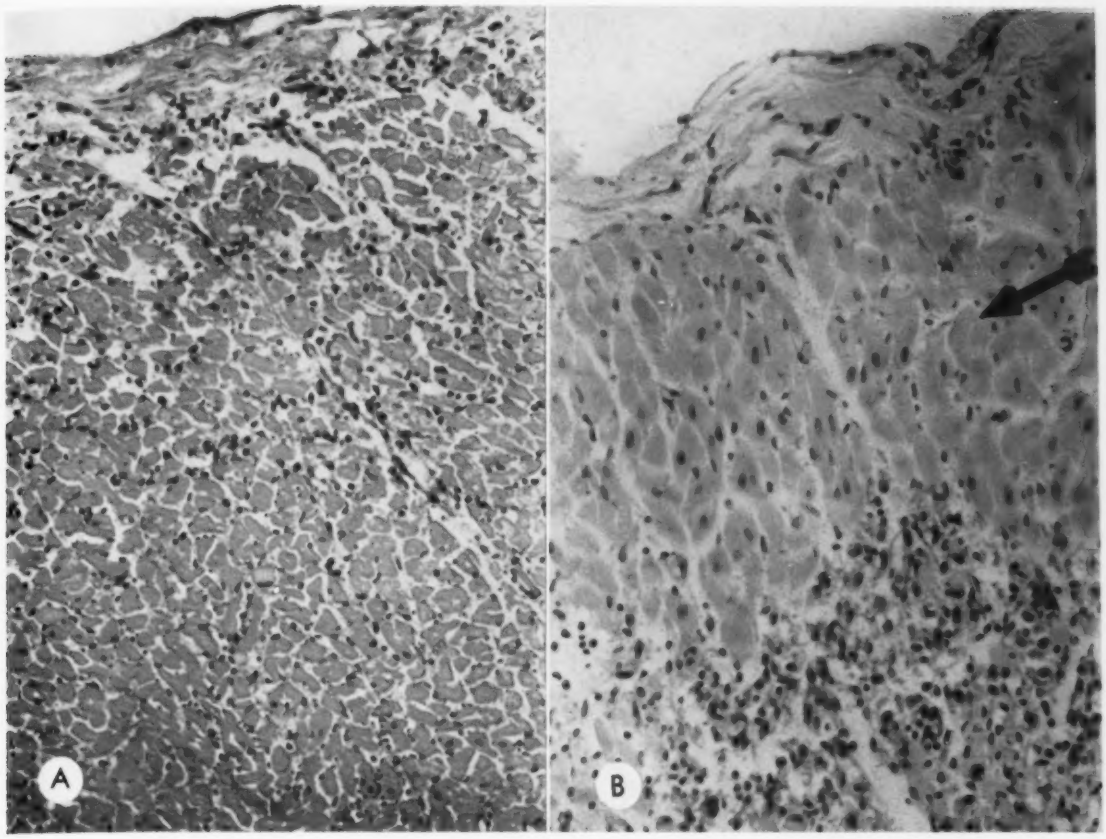

Fig. 7. (*A*) Photomicrograph of a section of infarcted ventricular wall in nonirradiated heart seven days post ligation of the anterior descending coronary artery. Necrosis extends to the epicardial surface. Hematoxylin-eosin stain ×196. (*B*) Comparable section of irradiated heart. Arrow is in region of spared normal muscle in subepicardium.

cardiograms showed no significant changes.

3. Blood studies (hemoglobin, hematocrit, white blood cell count, peripheral smear and iliac crest marrow examinations) showed no significant alterations, and were within normal limits.

4. All dogs were in good health when they were sacrificed.

5. Gross and microscopic findings revealed patchy areas of pleural thickening of both lungs underlying the portals of irradiation. There was no pleural effusion or evidence of radiation pneumonitis or pulmonary fibrosis.

6. No pericarditis, pericardial effusions, or gross myocardial damage was seen.

7. The coronary vessels were not obliterated.

8. The esophagus was grossly unremarkable (microscopic sections were taken and confirmed the above gross finding).

9. Sternal marrow in the irradiated area was as previously described. Normal hematopoiesis was seen in marrow obtained away from the irradiated area.

DISCUSSION

Previous studies[9,10,11] have shown that dogs receiving cardiac irradiation prior to left anterior descending coronary artery ligation have a higher rate of survival and greater intercoronary anastomotic blood flow than do nonirradiated animals. A pathologic analysis of equivalent irradiated and nonirradiated hearts is of great help in understanding the cause of the increase in the survival rate and in the coronary blood flow. Although the normal pattern of

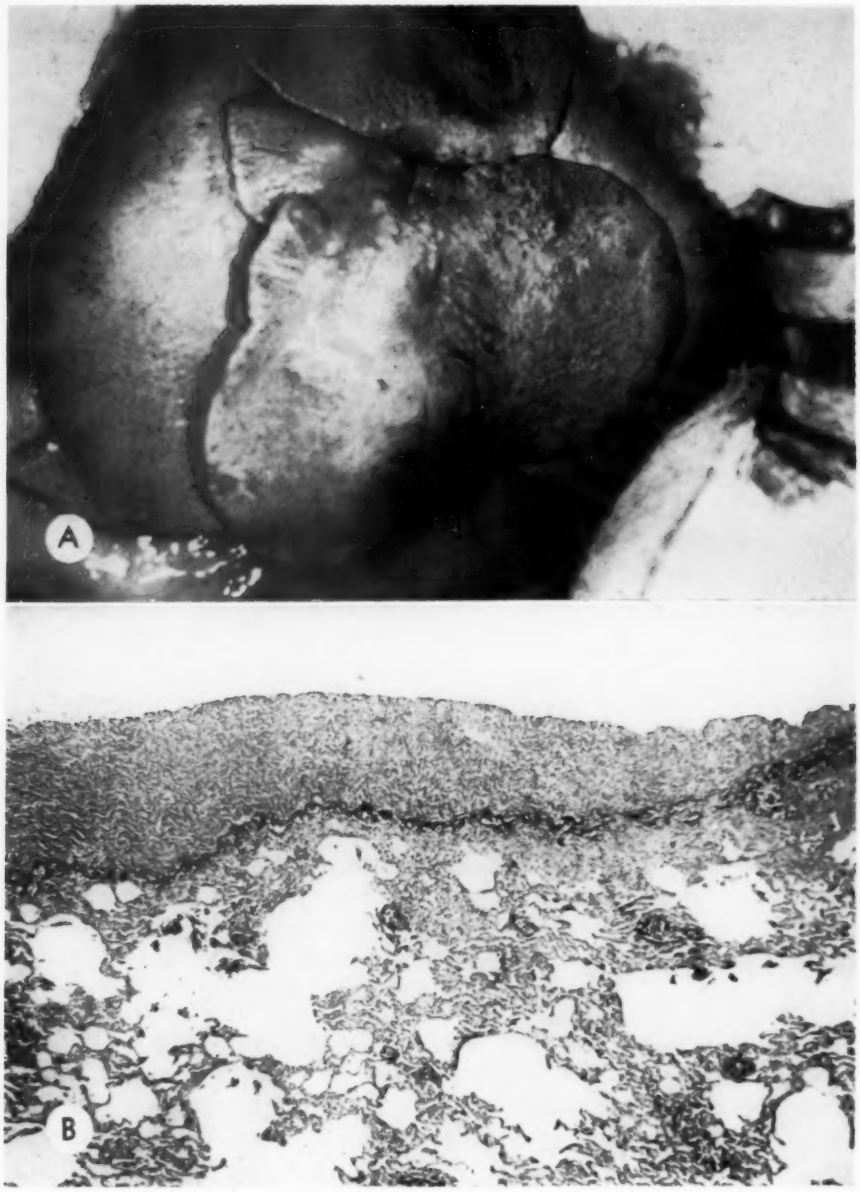

FIG. 8. (*A*) Photograph of dog's lungs taken at time of thoracotomy six months post irradiation (3,600 r). Several areas of pleural thickening are present. These changes are limited to the area of irradiation. The remaining pleural surfaces appear normal. (*B*) Photomicrograph of section of lung tissue underlying the field of irradiation (3,600 r) six months post irradiation. Note pleural thickening and small area of subpleural fibrosis. The elastic membrane of the pleura is intact. The remainder of the underlying lung tissue appears normal. Hematoxylin-eosin stain ×58.

coronary artery distribution to the heart physiologically amounts to an end arterial system,[12] anatomically the terminal ramifications of the coronary arteries are in mutual cross communication by way of a network of minute intercoronary vascular channels.[3,8,13] Husni and Simeone[9] reported that the changes associated with the formation of collateral circulation in the myocardium when a major artery is occluded are, for the most part, attributable to the establishment of an increased gradient of pres-

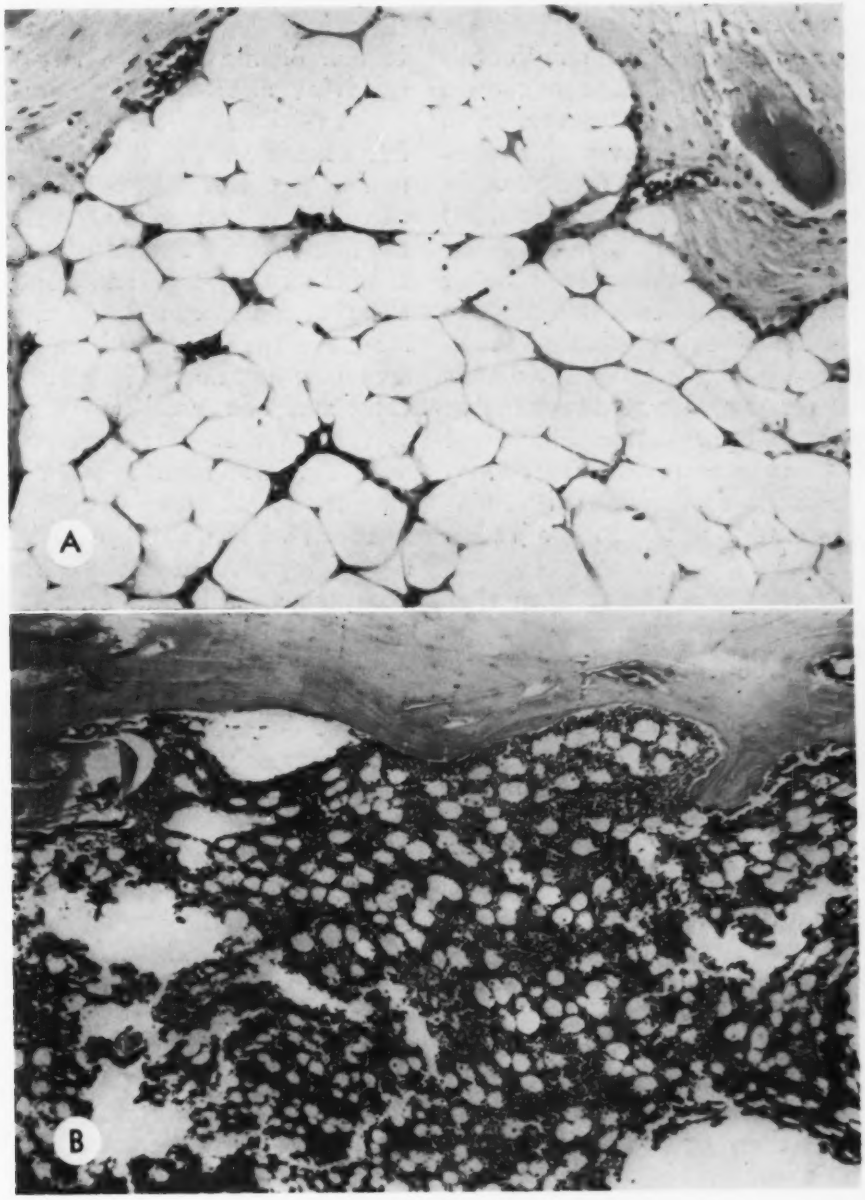

Fig. 9. (*A*) Photomicrograph of sternal marrow taken from irradiated field six months post irradiation (3,600 r). A focal area of hypocellular marrow is present. Hematoxylin-eosin stain ×196. (*B*) Photomicrograph of sternal marrow taken from area remote from field of irradiation six months post irradiation (3,600 r). Normal hematopoiesis is seen. Hematoxylin-eosin stain ×58.

sures between the intact arteries and the small intercoronary communicating vessels in the area immediately adjacent to the ischemic myocardium. Their data suggested that such preformed intercoronary anastomotic connections were available in the majority of dogs studied. Bellman and Frank[2] state that though this system of communicating vessels is present, there is normally no substantial flow through these collateral channels because of their high resistance to blood flow. They also state that no substantial flow through these channels is to be expected immediately following coronary occlusion despite the maximum pressure gradient resulting from

the occlusion. Survival then apparently depends upon the adequate functioning of this preformed intercoronary bed at the time of occlusion. It is believed that dilatation of any of these intercoronary vascular channels (terminal arterioles, intercoronary arterial vessels, venules, capillary bed) must necessarily be accompanied by similar dilatation of all the rest.[1] We postulate that successive small doses of radiation produce dilatation of the existing myocardial capillaries and precapillary arterioles and thus account for the demonstrated increase in survival rate and the evidence of increased blood flow. There was no evidence of formation of granulation tissue with subsequent new vessel formation at the doses of radiation administered.

In the present study it was seen that when the anterior descending coronary artery is ligated in a nonirradiated dog, a large area of myocardium, corresponding to the distribution of the ligated vessel, is deprived of the normal inflow of blood. All blood to this area must now enter in a retrograde fashion from branches of the left circumflex and right coronary arteries adjacent to the area of infarction. That this intercoronary anastomotic supply is functionally inadequate in the normal dog is demonstrated by the injection studies which show a bare area, devoid of barium or plastic, corresponding to the distribution of the anterior descending coronary artery. There were few, if any, intercoronary anastomotic connections open to permit the filling of this area in a retrograde fashion. Analysis, however, of the irradiated animals reveals the presence of functioning anastomotic channels through which barium and plastic flow in a retrograde fashion. The region of the myocardium supplied by the ligated vessel was thus filled and the bare area seen in the nonirradiated animals was not seen to the same extent. Irradiated hearts appeared in many cases to be completely vascular, despite the fact that the arterial inflow of a major vessel had been completely occluded.

Lumb and co-workers[6] have reported that following ligation of the anterior branch of the left coronary artery "the surviving animals had infarction of the entire thickness of the anterior wall of the left ventricle distal to the ligature." The nonirradiated dogs in our study exhibited this finding. However, of great interest is the fact that the irradiated hearts did not exhibit this "through and through" infarction, but contained a spared area of normal muscle in the subepicardium overlying the area of infarction. The presence of this extra area of normal muscle is important as regards the heart's ability to recover from the infarction. There is now a new dimension from which the reparative processes can occur. This also acts to accelerate the healing process. In the control dogs the necrotic area of infarction remained longer without being replaced by granulation tissue, and calcium was deposited in the necrotic muscle. In the faster healing irradiated dogs, there was much less opportunity for calcium deposition as the necrotic muscle fibers were absorbed by the healing process.

In the present study the cardiac irradiation was carried out directly through both lung fields. In the human application, an anterior chest field avoiding lung tissue could be used and thus the pleural effect noted at the higher radiation doses could be prevented.

SUMMARY AND CONCLUSIONS

1. Ligation of the anterior descending coronary artery has been performed on 66 dogs following varying doses of cardiac irradiation at varying intervals of time. A pathologic analysis of the hearts by means of injection and corrosion studies, and gross and microscopic examination has been carried out. Thirty control dogs, similarly ligated but not irradiated, were studied in the same manner. Nineteen irradiated animals, dying at varying intervals during and after radiation therapy (but prior to coronary ligation), were also studied.

2. The irradiated animals presented functioning intercoronary anastomotic chan-

nels at the time of coronary ligation.

3. A spared area of normal muscle was seen in the subepicardium overlying the area of infarction in the irradiated hearts. This finding was not observed in the nonirradiated control hearts.

4. Irradiated hearts healed faster than equivalent control hearts following myocardial infarction, as healing could occur from the spared area of normal muscle.

5. The effects of varying doses of cardiac irradiation upon the heart, lungs, bone marrow, hemogram and mediastinal tissues have been studied up to one year following irradiation. Evidence of focal radiation induced pleural and marrow changes directly under the field of irradiation was observed at some doses. The significance of these findings is discussed.

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The authors wish to express their appreciation to Dr. Harold Sobel, of the Department of Pathology, for his hematologic analysis of the irradiated animals.

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THE USE OF TRIMETHOBENZAMIDE (TIGAN) FOR THE TREATMENT OF RADIATION INDUCED NAUSEA AND EMESIS*

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NAUSEA and vomiting are frequent complications of radiation therapy. There is no universally accepted explanation of their etiology. The possible factors mentioned in the literature include: (a) toxic cellular disintegration products;[2] (b) destruction of intestinal mucosa following abdominal irradiation;[24] (c) choline poisoning;[15] (d) general debility and cachexia in a patient with advanced cancer;[21] (e) vitamin deficiency;[11] (f) histamine release;[5,6,12] (g) increased capillary permeability and a shock-like syndrome;[10] (h) chloride depletion;[13] and (i) psychic factors.[9]

It is not surprising that, with such variation in the suggested etiology, the recommended therapeutic measures are also extremely varied. Thus, in the past, good results have been claimed following the administration of: (a) sodium chloride;[21] (b) various members of the vitamin B complex,[8,16] especially pyridoxine;[18,22] (c) vitamin C;[6] (d) parenteral liver therapy;[4,26] (e) antihistaminics such as benadryl;[12] and (f) hormones, *e.g.*, desoxycorticosterone acetate[5] and ACTH.[23]

In recent years, much attention has been focused on drugs with a specific antiemetic action. Cyclizine (marezine)[22] and dimenhydrinate (dramamine)[19] and also many members of the phenothiazine group of drugs have been investigated. Among the latter, chlorpromazine (thorazine),[14] perphenazine (trilafon),[3] prochlorperazine (compazine)[20] and mepazine (pacatal)[22] have been studied. Drowsiness is a frequent side effect of all of these drugs. With some of the phenothiazine derivatives, especially thorazine, more serious side effects, such as hypotension and jaundice,[7] have been reported. The drowsiness that may accompany the use of these agents is especially undesirable when radiation therapy is carried out on outpatients.

Because of the possible undesirable side effects of the phenothiazine derivatives, it seemed worthwhile to investigate the therapeutic efficacy, in radiation induced nausea and emesis, of trimethobenzamide (tigan), a recently introduced antiemetic, chemically unrelated to the phenothiazines.

MATERIAL AND METHOD

The material for this study was selected from 276 consecutive patients undergoing cobalt 60 teleradiation therapy with skin doses ranging from 1,250–2,000 r per week and with treatment portals ranging from 5×5 to 12×20 cm. In an effort to eliminate some of the psychologic factors, no patient was told that nausea and vomiting might accompany the treatment. Only those patients who did not have nausea or vomiting prior to therapy and who complained spontaneously of this complication within the first ten days of treatment were included in the investigation. There were 54 such patients and these were arbitrarily divided into two groups. The 31 patients in the first group received 200 mg. of tigan four times daily, and the 23 patients in the second group received a placebo, designated "tigan X," which was identical in appearance with tigan. The technician allocating the drugs did not know which was the active drug and which the inert placebo.

Evaluation of the results was made forty-eight hours after the institution of medication by one of us (J.A.B.), who sim-

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ilarly did not know whether the antiemetic or the placebo had been administered to the patient. The identity of the medication was revealed only after the therapeutic results had been evaluated in all patients.

The intensity of the symptoms was graded as: (a) severe (severe nausea and frequent vomiting); (b) moderate (infrequent vomiting and/or moderate to severe nausea); and (c) mild (little nausea and no vomiting). For purposes of evaluation, the patients in both the tigan and placebo groups were divided according to the intensity of their symptoms into 3 subgroups each, corresponding to the response to treatment which was graded as follows: (a) complete; (b) partial; and (c) no relief.

RESULTS

As mentioned above, only 54 of the 276 patients (20 per cent) complained of vomiting and/or nausea within ten days of the commencement of the radiation therapy. It can be seen in Table I that the incidence of nausea and vomiting varied with the area irradiated. It was highest (38 per cent) after irradiation of the abdomen, less (22 per cent) after irradiation of the thorax, and least (5 per cent) after treatment of other parts of the body.

As is obvious from Table II, which shows the effectiveness of treatment, tigan produced some degree of relief in 80.6 per cent of the patients and failed to do so in 19.4 per cent. Contrariwise, placebo medication was helpful in 60.8 per cent of the cases and ineffective in 39.2 per cent. Of the 4 patients in the subgroup with severe symptoms who received tigan, 2 derived partial relief and 2 were not benefited. On the other hand, none of the 3 patients in the corresponding subgroup who were given the placebo showed any improvement. Furthermore, of the 21 patients with

TABLE I

INCIDENCE OF NAUSEA AND/OR VOMITING AFTER COBALT 60 TELETHERAPY

Area Irradiated	No. of Patients Irradiated	Incidence of Nausea and/or Vomiting (First Ten Days of Treatment)				
		Site of Lesion	Tigan Group	Tigan X (Placebo) Group	Total No. of Patients	Per Cent
Abdomen	53	Adrenal gland	0	1	20	38
		Bladder	2	3		
		Cervix	2	2		
		Kidney	1	1		
		Lumbar spine	1	1		
		Mesenteric lymph nodes	1	0		
		Ovary	3	1		
		Stomach	1	0		
Thorax	139	Breast	11	9	30	22
		Esophagus	2	0		
		Lung	4	3		
		Mediastinal lymph nodes	1	0		
Head Neck Extremities	84	Brain	0	1	4	5
		Epiglottis	0	1		
		Maxilla	1	0		
		Tongue	1	0		
Total	276		31	23	54	20

TABLE II

EFFECTIVENESS OF ANTIEMETIC TREATMENT

Intensity of Symptoms	Tigan						Tigan X (Placebo)					
	No. of Patients	Complete Relief		Partial Relief		No Relief		No. of Patients	Complete Relief		Partial Relief		No Relief	
		No.	Per cent	No.	Per cent	No.	Per cent		No.	Per cent	No.	Per cent	No.	Per cent
Severe	4	0	00	2	50	2	50	3	0	00	0	00	3	100
Moderate	21	12	57	6	29	3	14	12	1	08	7	59	4	33
Mild	6	5	83	0	00	1	17	8	6	75	0	00	2	25
Total	31	17	54.8	8	25.8	6	19.4	23	7	30.4	7	30.4	9	39.2

moderate symptoms who received tigan, 12, or 57 per cent, derived complete relief and only 3, or 14 per cent, were not benefited, but, of the 12 patients in the corresponding subgroup who were given placebo medication, only 1 patient, or 8 per cent, experienced complete relief and 4 cases, or 33 per cent, were not benefited. In the subgroups with mild symptoms the results with tigan were only insignificantly superior to those with placebo medication.

No side effects attributable to tigan were observed in this series.

DISCUSSION

It is evident, both from the results of this investigation and from the reports of other workers,[19,22] that teleradiation applied to the abdomen produced more nausea and vomiting than that encountered after irradiation of other regions. Furthermore, the nausea and vomiting were more severe and refractory to treatment after irradiation of this area. Similarly, the incidence and severity of symptoms appeared to be greater after long-term than after short-term therapy.[19]

The therapeutic efficacy of such variable measures as those summarized earlier in this paper suggests the importance of psychologic factors in radiation-induced nausea and vomiting. This is confirmed by the number of placebo reactors seen both in this and other series. For example, Stoll[22] reported 53 to 75 per cent relief with placebos. Consequently, when assessing the therapeutic value of different drugs, it is necessary to consider not only the degree of relief obtained from the drug and from a placebo, but also the site irradiated, the amount of radiation given, and the severity of the initial symptoms.

Solan[20] compared the antiemetic effect of compazine, pyridoxine and a placebo in 45 patients. He found that 16 out of 16, 11 out of 14 and 9 out of 15 patients obtained some degree of relief after compazine, pyridoxine or a placebo, respectively. Unfortunately, no information was given regarding the site and dose of irradiation or the intensity of the initial symptoms. Marks[14] reported good results in 84 out of 85 patients with thorazine, but control studies with a placebo were not included in this investigation. Where larger doses (50 mg.) of thorazine were given intramuscularly, drowsiness occurred in some patients.

Dickson[3] obtained excellent results with trilafon in a small number of cases. However, here again no information was given regarding site or dose of irradiation or severity of symptoms, and no controls were used.

The results reported with pyridoxine have been conflicting. In Shorvon's[18] series, without placebo controls, 90 per cent improvement was reported. In a study with

placebo controls, Stoll[22] reported 54 to 60 per cent relief with pyridoxine, but he also found improvement in 53 to 75 per cent after a placebo. Silverman *et al.*[19] found pyridoxine or a mixture of pyridoxine and dramamine to be no more effective than a placebo.

Stoll[22] obtained 55, 76 and 77 per cent relief with marezine, thorazine and pacatal, respectively, when the site of irradiation was below the diaphragm. Although no results with placebos are given for this group, the over-all relief after placebos, reported in the same paper, was 54 to 60 per cent. Stoll considered pacatal to be the most satisfactory of these drugs. Side effects, in this investigation, were limited to a few cases of drowsiness after thorazine.

If the cases with severe and moderate symptoms in this study are combined, 20 of 25 patients who received tigan and 8 of 15 patients who were given the placebo derived some degree of relief. These figures (80 per cent for tigan and 53 per cent for the placebo) are similar to those quoted for pacatal and a placebo.[22] While tigan failed to give complete relief in any case with very severe symptoms, it did give partial relief in 50 per cent of such cases. On the other hand, placebo medication consistently failed to give any relief in this type of case. More than one half of the patients with moderate symptoms were completely relieved with tigan, but only 1 of 12 patients who received placebo medication in the corresponding subgroup became asymptomatic. Since the degree of relief with pacatal is not mentioned in Stoll's[22] study, a comparison of his results and ours is not too meaningful.

The clinical impression of the radiologists (J.A.B. and C.R.P.) participating in this study was that tigan was as good, or better, than the other drugs (pyridoxine, compazine, etc.) they had previously used for the treatment of radiation induced nausea and emesis. The lack of side effects from tigan was greatly appreciated by patients and radiotherapists alike.

In another study,[25] 200 mg. tigan, administered intramuscularly 3 times at three hour intervals after surgery, was only moderately effective against postoperative nausea and vomiting, as compared with placebo injections. In contrast, Adriani *et al.*[1] reported that 50 mg. of tigan administered intravenously was 100 per cent effective in the treatment of severe postoperative nausea and emesis. Considerably larger doses (200 mg.) were also used without ill effects for the same purpose by other investigators.[17] In view of these findings, an investigation of the efficacy of tigan given intravenously for the treatment of radiation induced nausea and emesis will be undertaken.

SUMMARY

1. Of 276 consecutive patients treated with cobalt 60 teleradiation with skin doses ranging from 1,250 to 2,000 r per week, 54 complained spontaneously of emesis and/or nausea.

2. The incidence of vomiting and/or nausea was 38, 22 and 5 per cent following irradiation of the abdomen, thorax, and other parts of the body, respectively.

3. Of the 54 patients who developed vomiting and/or nausea, 31 received 200 mg. tigan by mouth four times daily, and 23 were given a placebo of identical appearance. The study was carried out with a double blind technique.

4. Tigan produced some degree of relief in 80.6 per cent of the patients and was ineffective in 19.4 per cent. The corresponding figures for placebo medication were 60.8 per cent and 39.2 per cent.

5. In patients with severe symptoms, neither tigan nor the placebo was completely effective. Whereas tigan gave partial relief in 50 per cent of these cases, no relief at all was obtained with the placebo. In patients with moderate symptoms, tigan gave complete relief in 57 per cent and partial relief in 29 per cent. The placebo gave complete relief in only 8 per cent and partial relief in 59 per cent. In patients with mild symptoms, tigan and the placebo were almost equally effective.

6. No side effects were encountered with tigan.

7. It is concluded that tigan is an effective antiemetic in radiation induced nausea and vomiting.

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SPLENIC SCINTILLATION SCANNING*

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THE human spleen, roentgenologically homogeneous and lacking an opacifiable lumen, has not proved susceptible to satisfactory detailed roentgenologic study. It is chiefly by indirect evidence that splenic size and configuration may be evaluated. Opacification of the spleen with thorium dioxide has been virtually abandoned because of late sequelae. Splenoportography demonstrates the splenic veins but very little of the spleen itself. Colloidal gold-198 is concentrated by reticuloendothelial tissue wherever it lies and consequently has been used to demonstrate the spleen by scintillation scanning, but never without the unwanted accompanying image of the liver which itself traps much of the radioactive colloid. Further, the amount of gold-198 taken up by the normal spleen is said to be insufficient for clinical scintillation scanning.[1]

In a previous report[5] we have outlined the practicality of splenic scintillation scanning, without interference from hepatic radioactivity, by an atraumatic method which causes selective splenic uptake of radioactive red blood cells. We have since acquired experience with a second method which, like the first, is a means of modifying red blood cells so that they are trapped within the physiologic "filters" of the spleen and liver. Because its "filter" is the more efficient, the spleen acquires a considerably greater concentration of sequestered red blood cells than does the liver. We have reviewed both methods in detail elsewhere.[6] Briefly, normal red blood cells may be modified for trapping either by coating (*i.e.*, sensitizing) D-positive cells with high-titer human anti-D serum, or by heating the cells at 49.8°C. for 15 minutes (Fig. 1). Either isologous or compatible homologous red blood cells may be used. The heated cell technique, a clinically simple procedure, has significant advantages over the sensitization method. It is applicable to all subjects regardless of Rh genotype, affords less opportunity for contamination of red blood cells, requires only 30 minutes for preparation including

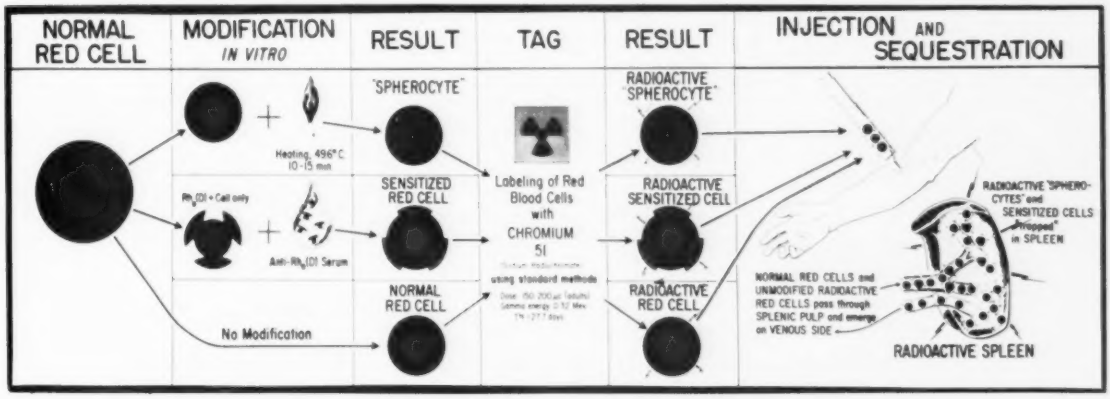

FIG. 1. Schematic illustration of methods of red blood cell preparation for splenic scintillation scanning.

* From the Department of Radiology, School of Medicine, University of North Carolina, Chapel Hill, North Carolina. This investigation was supported by U. S. Public Health Service Grant Number A-1996 (C1).

Presented at the Sixty-first Annual Meeting of the American Roentgen Ray Society, Atlantic City, New Jersey, September 27–30, 1960.

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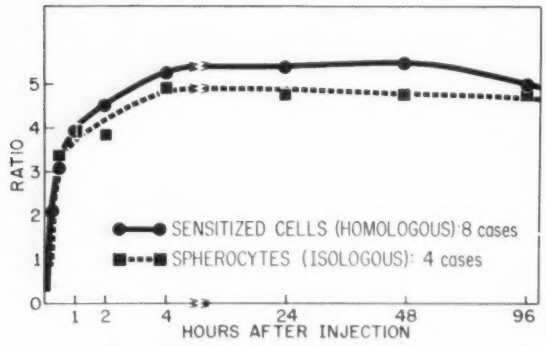

FIG. 2. Ratio of detectable splenic and hepatic radiation (S:L ratio) after administration of modified radioactive red blood cells.

addition of the chromium-51 label and results in a more rapid uptake of red blood cells by the spleen. Heating red blood cells in this manner increases their osmotic fragility, causing swelling of the cells and deformity into spheroidal forms which may in turn become microcytes by a type of fission.[2] These abnormal cells presumably become trapped in the splenic pulp after transfusion. The present study has shown the heated cell method to be applicable also to abnormal red blood cells from patients with sickle cell anemia and hereditary spherocytosis.

The relative splenic and hepatic uptake of transfused radioactive red blood cells is expressed as the spleen:liver ratio (S:L ratio) (Fig. 2). Scintillation probes are used to measure the detectable radiation in counts per minute at the skin over the spleen, liver and thigh. The thigh "count," an approximation of circulating or body background radioactivity, is subtracted from the gross spleen and liver "counts" to yield net values of the latter.

The rate of clearance of transfused radioactive red blood cells may be inferred from serial measurements of "body background" radiation, but quantitation of the red blood cell clearance (or survival) curve requires *in vitro* measurements of the amount of radioactivity per milliliter of red blood cells in serial samples (Fig. 3).

The scintillation scan may adequately be recorded by conventional printout on carbon-backed paper; however, we have preferred the photoscan technique because it allows contrast amplification, increases the appreciation of splenic configuration and permits later superimposition of the roentgenographic image of the spleen. The "dot" scan is useful as a visual monitor during the scanning process. In this investigation we employed a 2-inch scintillation crystal with cylindrical collimator, thus obtaining high sensitivity at the expense of relatively low resolution.

THE NORMAL SPLEEN

Our concept of the normal splenic scintiscan is based on experience with adult subjects without clinical or laboratory evidence of splenic disease (Table 1). Sensitized red blood cells were used in 8 cases, heated red blood cells in 4. The normal spleen and liver acquire radioactivity rapidly after transfusion. A greater concentration of

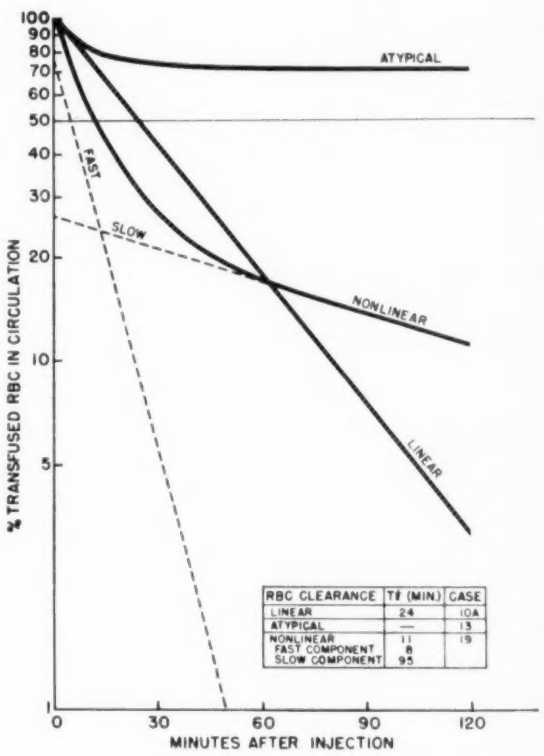

FIG. 3. Representative curves illustrating clearance of modified radioactive red blood cells from the circulation.

TABLE I

SELECTED DATA FROM CLINICAL STUDIES

Case, Age, Race, Sex	Disease Affecting Spleen	Dose Cr^{51} (μc)	Transfused Red Blood Cells					Length of Study (da.)	S:L Ratio at (hr.)	Area of Spleen (cm^2.)	Remarks
			Description*	Modified by	Half-Life (min.)	Clearance Curve	Reaction				
1. 57 CF	None	200	H D+	Serum	48	Linear	o	5	5.8:1 (24)	—	No scan (refused by patient)
2. 43 CF	None	200	H D+	Serum	98	Linear	o	19	5.6:1 (24)	70	
3. 54 CM	None	200	H D+	Serum	11	Nonlinear	o	56	1.9:1 (24)	—	No scan (atypical sequestration pattern)
4. 62 CM	None	200	H D+	Serum	47	Linear	o	70	6.3:1 (24)	80	
5. 26 CM	None	200	H D+	Serum	27	Linear	o	26	2.9:1 (24)	70	
6. 56 CM	None	200	H D+	Serum	24	Linear	o	2	5.6:1 (24)	60	
7a. 36 CM	None	150	H D+	Serum	49	Linear	o	33	4.6:1 (24)	60	Initial study
7b. 36 CM	None	150	I	Heat	30	Nonlinear	o	36	3.7:1 (24)	60	Repeat study at 7 mo.
8. 53 WM	None	150	H D+	Serum	50	Nonlinear	o	11	5.4:1 (24)	60	
9. 48 WM	None	150	H D+	Serum	34	Linear	o	24	8.4:1 (24)	80	
10a. 55 CM	Myelofibrosis	250	I	Serum	24	Linear	o	11	?	160	Initial study. Recent Fe^{59}
10b. 55 CM	Myelofibrosis	150	I	Serum	—	—	o	2 hr.	5.5:1 (2)	120	Repeat study after roentgen therapy
11. 58 WF	Chronic Granulocytic Leukemia	150	I	Serum	—	—	o	2 hr.	8.8:1 (2)	220	Splenomegaly (clinically uncertain) proved by scan
12. 41 WF	1° Splenomegaly	150	I	Serum	21	Linear	o	4 hr.	8.5:1 (4)	180	Splenomegaly (clinically uncertain) proved by scan
13. 42 WM	Lymphosarcoma	200	I	Heat	?	Atypical	o	30 hr.	5.4:1 (24)	120	Insufficient heating. Only 29% of tagged RBC was cleared
14. 62 WM	Lymphoblastic Lymphoma	200	I	Heat	20	Nonlinear	o	55	7.2:1 (24)	80	Splenomegaly (clinically diagnosed) disproved by scan
15. 62 WM	Fatty Metamorphosis, Liver	150	I	Heat	?	Atypical	o	1	2.8:1 (24)	—	No scan. Insufficient heating. Only 20% of tagged RBC was cleared
16. 66 WF	"Thorotrast" Spleen	200	I	Heat	—	—	o	44	2.9:1 (24)	20	
17. 76 WM	Chronic Lymphocytic Leukemia	200	I	Heat	4.3	Nonlinear	o	2	8.3:1 (24)	160	
18. 27 WF	Hereditary Spherocytosis	150	I	Heat	—	—	o	1	2.7:1 (24)	110	Scan of resected spleen (340 gm.)
19. 66 WM	None	200	I	Heat	11	Nonlinear	o	25	5.7:1 (24)	60	
20. 80 CM	None	200	I	Heat	32	Nonlinear	o	25	5.0:1 (24)	40	
21. 66 CM	None	200	I	Heat	20	Nonlinear	o	25	4.3:1 (24)	50	
22. 28 WM	Laennec's Cirrhosis	185	I	Heat	—	—	o	42 hr.	19.0:1 (42)	100	
23. 32 WF	Chronic Granulocytic Leukemia	500	I	Heat	—	—	o	4 hr.	?	—	Recent Fe^{59}. Unsatisfactory scan
24. 40 WF	Laennec's Cirrhosis	200	I	Heat	—	—	o	4	22.0:1 (24)	120	
25. 22 WM	Lymphoblastic Leukemia	200	I	Heat	—	—	o	2	10.2:1 (17)	110	
26. 11 WF	Hereditary Spherocytosis	125	I	Heat	—	—	o	2	5.5:1 (24)	70	Scan of resected spleen (144 gm.)
27. 6 CM	Sickle Cell Anemia	100	I	Heat	—	—	o	3	10.8:1 (72)	60	
28. 28 CM	Sarcoidosis	145	I	Heat	—	—	o	2	8.5:1 (24)	180	
29. 30 CM	Sickle Cell Anemia	200	I	Heat	—	—	o	24	0.5:1 (24)	—	No scan (hypofunctioning spleen)
30. 54 WF	Laennec's Cirrhosis	200	I	Heat	—	—	o	22	18.9:1 (24)	110	

* H—homologous. I—Isologous.

radioactivity within the spleen becomes evident within 15 minutes. Reflecting this, the S:L ratio rises progressively to an average value of 5.3:1 (range 2.9–8.4:1) at four hours. At this time virtually all radioactive cells have been cleared from the circulation.

Maximum splenic radioactivity is reached between 24 and 48 hours after transfusion, and the average peak S:L ratio of 5.5:1 occurs at 48 hours. Thereafter physical decay plus exponential release of chromium from the spleen and liver cause a gradual steady decrement of radioactivity in these organs. Splenic scintillation scanning is best performed between the 4th and 48th post-transfusion hour, although it may be done at 2 hours or as late as 7–8 days.

The normal splenic photoscan (Fig. 4, *A* and *B*) reveals an area of nearly homogeneous density on the film; the density is maximal centrally. This area is defined by relatively sharp margins and its configuration fits the familiar roentgenologic depiction of the frontal projection of the spleen. The splenic image is variably rounded or ovoid but not circular. The splenic "notch" has not been demonstrated. The scanographic and roentgenographic images are virtually superimposable. On the posterior photoscan the normal spleen has an approximate mean area of 60 sq. cm. (range of 40 to 80 sq. cm.).

THE ABNORMAL SPLEEN

Nineteen studies have been performed in 18 patients with various diseases of the spleen. In each case the diagnosis was established definitively by appropriate methods (Table 1).

(a) *Hereditary Spherocytosis.* In 2 female patients hospitalized for hereditary spherocytosis, preoperative splenic scintiscans confirmed clinically noted splenomegaly and demonstrated homogeneous distribution of radioactivity in the enlarged spleens. Each patient was given isologous heated cells, augmenting the existing

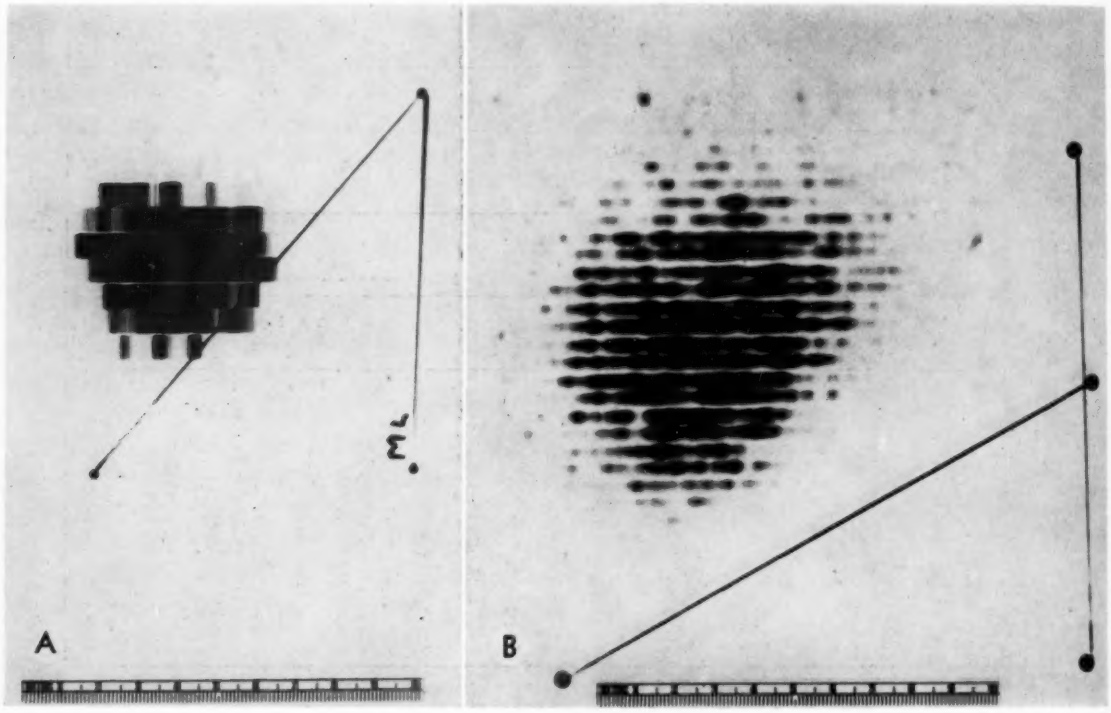

Fig. 4. (*A*) Lower (Case 20) and (*B*) upper (Case 9) limits of normal spleen size as demonstrated in the posterior photoscan.

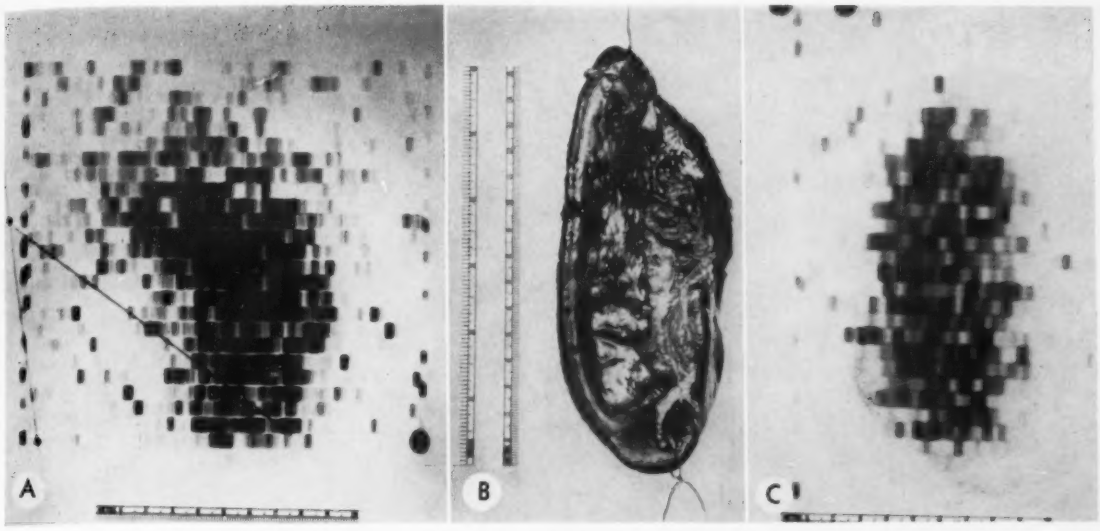

Fig. 5. Case 18. Hereditary spherocytosis. (*A*) *In vivo* photoscan shows splenomegaly. Compare with photograph (*B*) and photoscan (*C*) of resected spleen.

spherocytosis without macroscopic evidence of hemolysis. An eleven year old patient (Case 26) exhibited a 24 hour S:L ratio of 5.5:1, whereas a ratio of 2.7:1 was found in a twenty-seven year old patient (Case 18) (Fig. 5, *A*, *B* and *C*). Immediately after splenectomy the intact spleens were obtained for scintillation scanning. These scans demonstrated an essentially uniform dispersion of chromium-51 throughout the organ in each instance. Further, they confirmed the intrasplenic location of the chromium 51 and indicated the resolving capabilities of the cylindrical collimator.

(b) *Sickle Cell Anemia.* Two Negro males with sickle cell anemia, aged six years and thirty years, were studied with isologous heated cells. Limited study of the child (Case 27) using 100 μc of chromium-51 produced a 72-hour S:L ratio of 10.8:1, confirmed the presence of splenomegaly and showed uniform distribution of splenic radioactivity (Fig. 6). In the adult patient (Case 29), however, the S:L ratio at 24 hours was 0.5:1. Inversion of the ratio persisted without change during three and a half weeks of observation. Net splenic radioactivity remained low and no scan was performed. This patient's spleen was not palpable clinically nor visible roentgenologically. Measurement of body background levels suggested that the red blood cell clearance rate was unusually slow.

These patients represent widely separated clinical stages of sickle cell anemia, the adult patient having advanced well toward the condition of autosplenectomy.

(c) *Leukemia—Lymphoma.* Of 6 patients

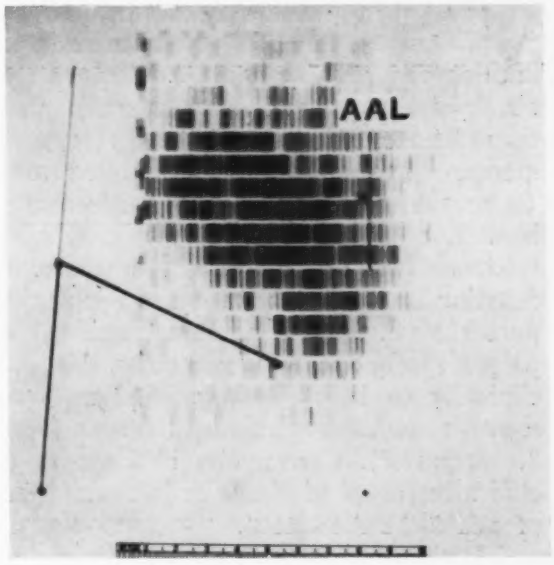

Fig. 6. Case 27. Sickle cell anemia with splenomegaly in a six year old child.

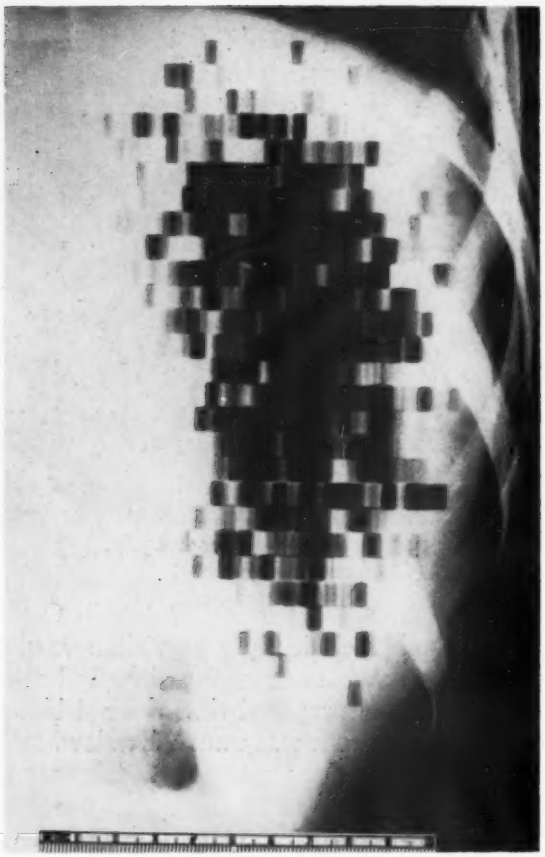

Fig. 7. Case 25. Acute lymphoblastic leukemia. Photoscan-radiograph shows predominantly central distribution of radioactivity in the enlarged spleen.

in this group, satisfactory splenic scans were obtained in 5, and splenomegaly was demonstrated in 4 (Fig. 7). The S:L ratios, measured at various intervals, ranged from 5.4 to 1 to 10.2 to 1. Both sensitized and heated cells were used. The enlarged spleens exhibited apparently homogeneous distribution of radioactivity throughout the parenchyma. In one patient (Case 14) a palpable left upper quadrant mass, thought clinically to be an enlarged spleen, was shown to be extrasplenic by the scan (Fig. 8, *A* and *B*). Conversely, in Case 11 a clinically atypical left-sided mass was proved to be the spleen.

Selective splenic uptake of isologous heated cells failed to occur in a thirty-two year old female (Case 23) with chronic granulocytic leukemia and massive hepatosplenomegaly. An unsatisfactory scan showed faint, equal density of each organ.

(d) *Hepatic Disease.* Of 4 patients in this group, failure to obtain a satisfactory splenic scan occurred in one (Case 15), a sixty-two year old male with fatty metamorphosis. In this case there was intentional inadequate heating of isologous red cells. That only a portion of these cells became morphologically abnormal is suggested by the atypical red blood cell clearance curve which leveled into a plateau at the 80 per cent level 10 minutes after transfusion. In 3 patients having Laennec's cirrhosis (Cases 22, 24, 30), very high S:L ratios occurred and satisfactory splenic scans were made. Each scan demonstrated splenomegaly with essentially homogeneous distribution of radioactivity. Lateral scans in 2 cases presented the splenic image in sagittal projection and demonstrated an anterior concavity (? liver impression) in one (Fig. 9, *A* and *B*).

(e) *Other Diseases.* Four patients with miscellaneous diseases are included in this group. Clinical splenomegaly was confirmed by splenic scan (Fig. 10, *A* and *B*) in an elderly male with myelofibrosis (Case 10). Shrinkage of the spleen was demonstrated by a repeat scan after completion of local roentgen ray therapy.

Splenomegaly with nonuniform distribution of radioactivity was demonstrated in a twenty-eight year old Negro male (Case 28) with systemic sarcoidosis (Fig. 11). A homogeneous splenic photoscan was obtained in a forty-one year old white female (Case 12) with slight splenomegaly of indeterminate etiology; clinically, the presence of splenic enlargement had been equivocal. In the final patient (Case 16), a sixty-six year old white female, thorium dioxide had been employed for carotid arteriography seven years earlier, and roentgenologically the spleen was shrunken and opacified. Diminution of splenic function was suggested by a 24 hour S:L ratio of 2.9:1, but a satisfactory photoscan was obtained. This demonstrated a splenic area

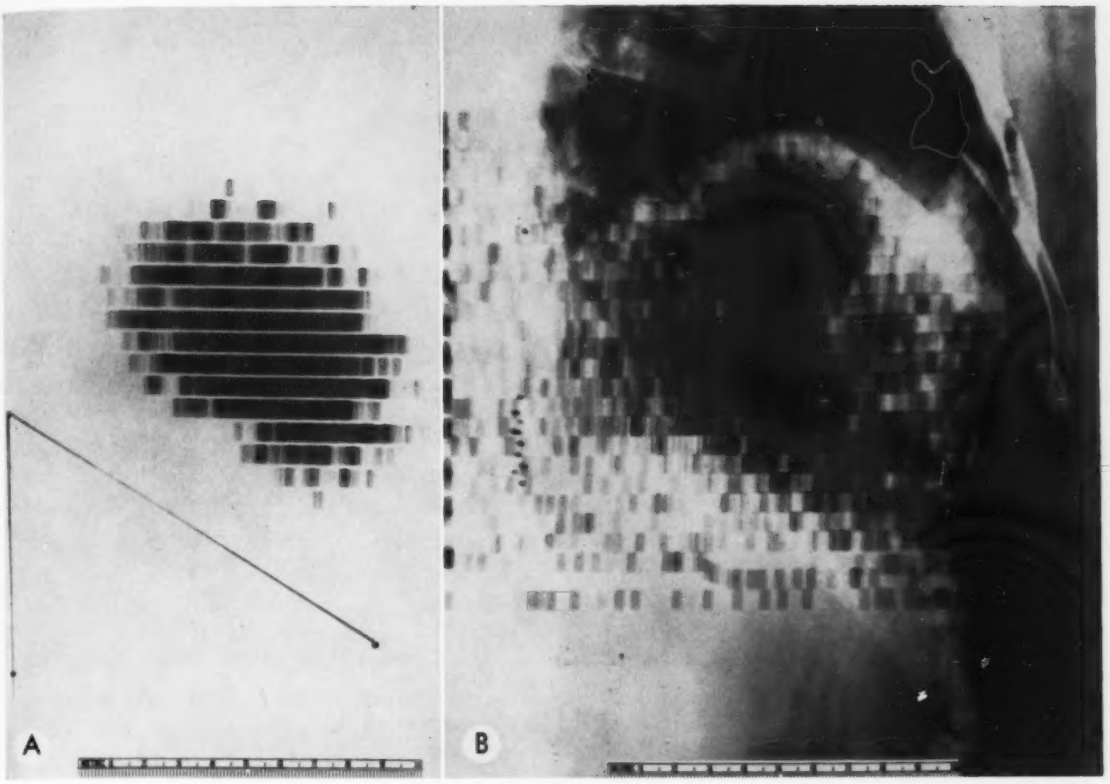

Fig. 8. Case 14. Lymphoblastic lymphoma. (*A*) Photoscan and (*B*) photoscan-radiograph. Clinically diagnosed splenomegaly was disproved by scan; left upper quadrant mass was extrasplenic.

of only 20 sq. cm. Of interest was the location of the splenic photoscan image *below* the opaque roentgenologic image on the combined photoscan-radiograph (Fig. 12, *A* and *B*). A conceivable explanation for this discrepancy is that an accessory spleen had formed after the thorotrast insult to the primary spleen and was the source of radioactivity.

HAZARDS

No untoward or undesirable reaction was observed in this investigation. The potential hematologic hazards are virtually negligible. Using ABO- and Rh-compatible red blood cells, the danger of inducing significant antibody formation is minimal. Nevertheless, it may be eliminated by using the patient's own cells. *In vivo* red blood cell coating by excess (unbound) anti-D serum in the transfused red blood cell suspension is preventable by washing the cells after sensitization. Even the remote possibility of hemolysis of all transfused blood should have no significant clinical effect since only 6 to 8 ml. of red blood cells are administered.

The amount of radiation delivered to the whole body, the liver and spleen, and the gonads depends on the variable factors of chromium-51 dosage, rapidity of red blood cell clearance, relative concentration of sequestered cells in the liver and spleen, the masses of these organs and their distance from the gonads.

Using reasonable assumptions based on data derived from this investigation, the calculated *total radiation doses* to various tissues after administration of 150 μc of chromium-51 bound to modified red blood cells are as follows: the *whole body* receives not more than 54 millirads; the *ovary* receives 63 millirads; the *testis* receives 18.5 millirads; the *liver* receives 319 millirads;

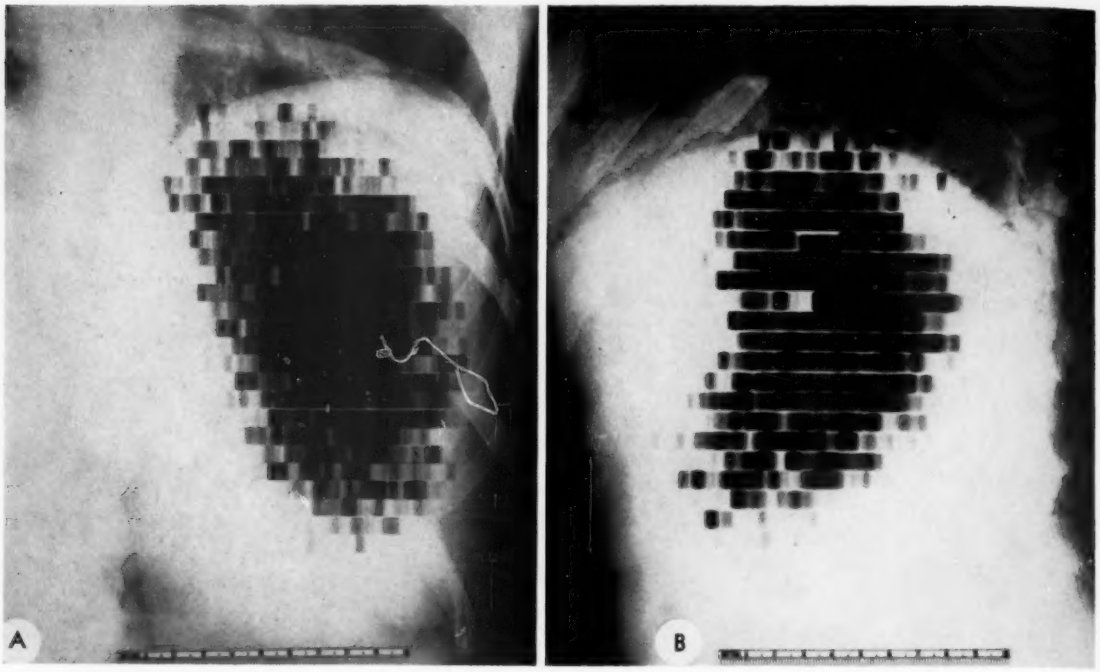

FIG. 9. Case 24. Laennec's cirrhosis with hepatosplenomegaly. (*A*) Frontal and (*B*) lateral photoscanradiographs reveal location of enlarged spleen and homogeneous distribution of radioactivity.

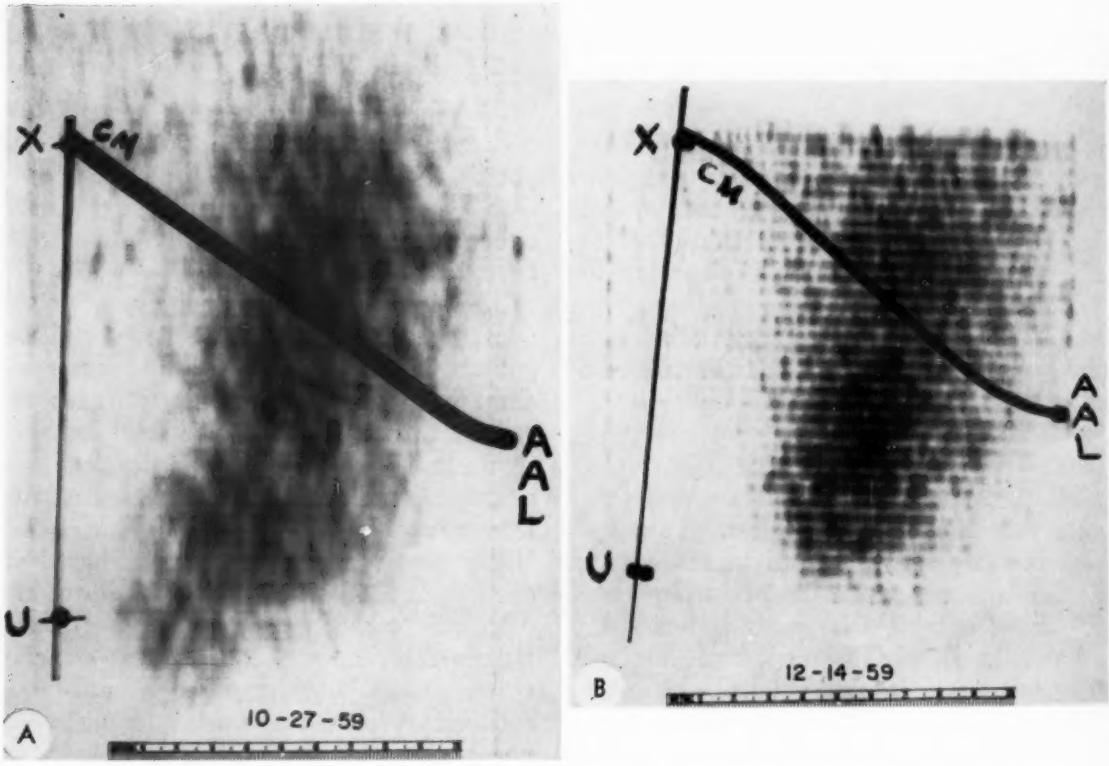

FIG. 10. Case 10. Myelofibrosis with marked splenomegaly. Anterior photoscans show (*A*) initial enlargement of spleen and (*B*) shrinkage of organ after roentgen irradiation.

and the *spleen* receives 10.7 rads.* The spleen, sequestering the majority of the radioactive red blood cells, acquires the greatest amount of radiation. The total splenic dose of 10.7 rads may perhaps be compared to the dose delivered to a 40 gm. thyroid gland taking up 9 μc of iodine-131 with an effective half-life of 5.5 days; under these conditions the thyroid gland receives a total dose of 19 rads.

DISCUSSION

On the basis of this investigation an assessment of the clinical value of splenic scintillation scanning can be made. The splenic scan objectively demonstrates the size, location and configuration of functioning splenic tissue. This delineation lacks the high resolution of which roentgenologic methods are capable, a disadvantage which is offset by the frequency with which a complete splenic image is seen. The splenic scan is valuable in the differential diagnosis of mass lesions of the left upper abdomen, as in Case 11 and 14, and permits a positive statement concerning the presence or absence of splenomegaly, as in Case 12. The splenic scan may permit identification of accessory splenic tissue; only further experience will clarify this possibility. This statement also applies to the use of red blood cell trapping for rapid localization of the small or slightly enlarged spleen prior to splenoportography.

Except for one patient with sarcoidosis, the available clinical material did not provide an opportunity to study discrete intrasplenic granulomata or other localized lesions; the volume of such lesions would largely determine whether they would be detected by a low-resolution collimator. However, focal intrasplenic lesions not only are uncommon but lack the significance of nonfunctioning hepatic and thyroidal nodules, the differential diagnosis of which frequently must include the possibility of neoplasia.

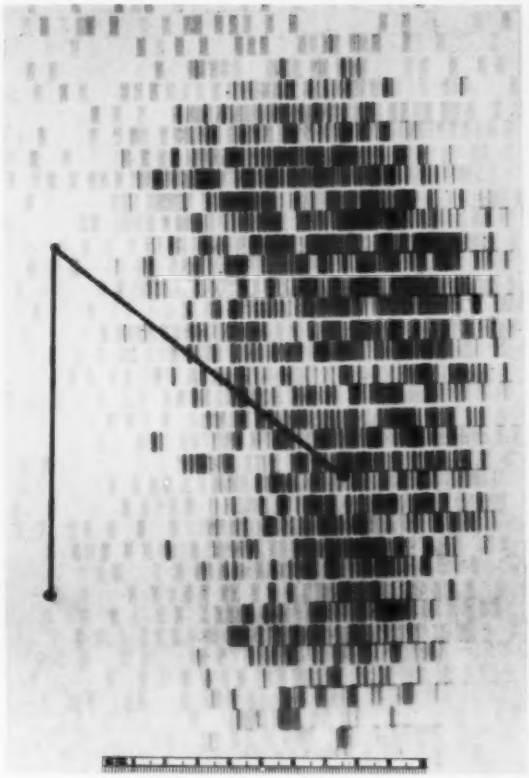

Fig. 11. Case 28. Sarcoidosis with splenomegaly. Nonhomogeneous distribution of radioactivity suggests partial replacement of functioning parenchyma by granulomata.

Two interrelated aspects of the splenic scanning procedure require additional investigation. A semilogarithmic plot (Fig. 3) of radioactive red blood cell clearance yields either a linear curve, reflecting the action of a single exponential function, or a nonlinear curve. Nonlinear curves can usually be resolved into two linear components of varying slope, indicative of two exponential processes acting simultaneously at different rates. We have observed linear and nonlinear curves in both normal subjects and patients with splenomegaly when sensitized cells were used, but have without exception seen only nonlinear curves when isologous heated cells were employed. Harris *et al.*[3] believe that the two components of the nonlinear clearance

* The assumptions employed in these calculations were: (1) 5/6 of the administered dose of 150 μc of chromium 51 enters the spleen and 1/6 enters the liver, with homogeneous distribution of the nuclide in each organ; (2) the effective half life of chromium 51 in the spleen and liver is 16.4 days and 21.8 days respectively; (3) the normal spleen and liver weigh 150 gm. and 1,700 gm. respectively; their effective centers are 25 cm. apart; (4) the distance from spleen or liver to the ovary is 30 cm. and to the testis is 40 cm.

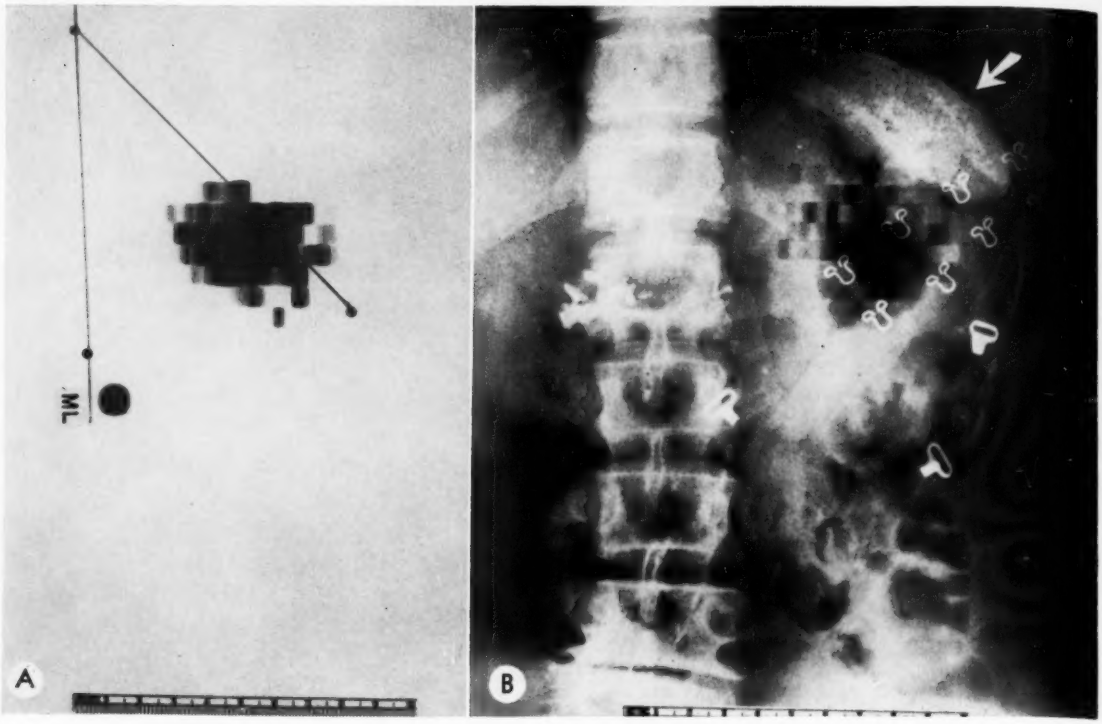

Fig. 12. Case 16. "Thorotrast spleen." (*A*) Note reduced area of splenic radioactivity and (*B*) its position below the contracted opaque spleen (arrow) on the photoscan-radiograph.

curve correspond to the rates of blood flow through two splenic "compartments," the closed or sinusoidal circulation and the open or pulp circulation. However, Weiss[7] has recently questioned the existence of an extrasinusoidal circulation in the human spleen. Hughes Jones *et al.*[4] postulate that the "fast" and "slow" components of the nonlinear clearance curve correspond respectively to intrahepatic and intrasplenic sequestration of red blood cells. Although the form, slope and half-survival time of the red blood cell clearance curve are determined in part by the type of red blood cell and its specific modification, these features presumably reflect as well the still-obscure processes of red blood cell removal and destruction.

The spleen:liver ratio is a measure of the relative activity of a physiologic process common to both organs. In this sense the ratio appears to have value as a clinical index of splenic and hepatic function. Unavoidable geometric errors affect any external determination of the concentration of radioactivity in two organs differing tenfold in mass; nevertheless the S:L ratio in our hands has been useful in measuring the splenic red blood cell trapping function. The upper limit of the range of the normal ratio probably does not exceed 10 to 1. We lack sufficient material to define the lower limit which may be 2 or 3 to 1. Of the diseases studied, only Laennec's cirrhosis with splenomegaly was associated with a significantly elevated S:L ratio. Our data suggest that the elevation resulted largely from decreased hepatic red blood cell sequestration, and raise the possibility that ratio measurement may have usefulness in the evaluation of cirrhosis and other hepatic diseases.

A feature of the S:L ratio observed in some cases was an often pronounced tendency toward fluctuation during the phase of red blood cell clearance. Whereas small changes may have been caused by such external factors as minor shifts in place-

ment of the scintillation probes, major fluctuations could reasonably be attributed only to real changes in the rates of splenic and hepatic sequestration. In Case 3, for example, it would be of interest to learn why an S:L ratio of 5.0:1 at 15 minutes had fallen to 1.9:1 at 24 hours. In this patient, who had no evidence by the usual criteria of splenic dysfunction, the clearance of the homologous sensitized red blood cells was nonlinear with a half-survival time of 11 minutes, an unusually low value. Future correlations of ratio measurements with red blood cell clearance curves may clarify the significance of these and similar findings.

SUMMARY AND CONCLUSIONS

These conclusions may be drawn from the present investigation of splenic scintillation scanning in a series of patients with normal or diseased spleens:

1. The splenic scintillation scan satisfactorily demonstrates the size, position and configuration of the functioning spleen without interference from hepatic radioactivity. It establishes the presence or absence of splenomegaly and thereby permits differentiation of mass lesions in the left upper abdominal area.

2. The technique of preparing red blood cells for the scanning procedure is clinically practical. There is no hematologic hazard to the recipient. The total radiation dose compares favorably to the amounts of radiation delivered in accepted clinical procedures using radioactive isotopes.

3. Further applications of splenic scintillation scanning may include the identification of accessory splenic tissue and the localization of the impalpable spleen for procedures requiring splenic puncture.

4. Measurement of the relative concentration of radioactivity in the spleen and liver has potential value as an index of a function common to these organs.

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EVALUATION OF LIVER FUNCTION WITH RADIOACTIVE IODIPAMIDE*

By JOHN R. McLAREN, M.D., JOHN T. GALAMBOS, M.D., *and* H. STEPHEN WEENS, M.D.
ATLANTA, GEORGIA

SINCE Graham and Cole introduced the first roentgenographic contrast medium for evaluation of the biliary tract, a large number of oral compounds have been perfected. These have proved remarkably nontoxic and so efficient that roentgenography of the biliary tree is one of our most accurate examinations. The search for a compound which could be safely administered intravenously and which would be sufficiently concentrated by the liver to yield a satisfactory cholangiogram was less rewarding. Not until Langecker *et al.*[4] introduced a new chemical compound in 1953 was such an agent available. Soon thereafter Frommhold[1] and Hornykiewytsch and Stender[2] demonstrated the value of this compound for intravenous cholangiography. This compound has since been widely applied in medicine and in this country is more commonly known as Cholografin.

Frommhold noted that the urinary excretion of iodipamide was greater in patients with liver disease than in patients without liver disease. Numerous observations have been made as to a correlation between laboratory evidence of liver dysfunction and failure of opacification of the biliary tree on intravenous cholangiography. These experiences suggested that radioactive iodipamide, which can be easily assayed, might be used for a sensitive evaluation of liver function. A number of dogs was studied before and after liver damage was produced with either the inhalation of carbon tetrachloride or the surgical obstruction of the common bile ducts.[6] A striking decrease in the hepatic radioactive uptake was noted after the production of liver damage. The present study is of similar work on patients with and without liver disease and includes special applications of this technique.

PROCEDURE

Hospital patients were divided into two groups. One group consisted of patients with liver disease proved by clinical and laboratory means. A number of these had liver biopsies. The control group comprised patients admitted to the medical and surgical services without laboratory or clinical evidence of liver disease.

After an overnight fast, the patients were placed in the supine position and scintillation detectors were positioned over the heart and liver. The hepatic monitor was placed at the midclavicular line 3 cm. cephalad to the lower costal margin. Approximately 3 cm. clearance was permitted between the probe and the skin surface. The probe was a Nuclear Chicago model no. DS-5, serial no. 378, to which no additional collimation was added. An intravenous dose of 1 ml. of iodipamide per 40 pounds of body weight was administered. This contained approximately 15 μc of radioactivity. The change in radioactivity over the heart and liver was recorded by means of count rate meters and chart recorders for time intervals of approximately 10 to 15 minutes. An aliquot of blood was withdrawn after a 3 hour interval. Three and 24 hour urine and 48 hour stool collections were made.

Preliminary hepatic uptakes were obtained on patients to determine whether or not any correlation existed between the

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This work is supported by AEC Contract No. AT-(40-1)-2675.
Presented at the Sixty-first Annual Meeting of the American Roentgen Ray Society, Atlantic City, New Jersey, September 27–30, 1960.

hepatic uptake of the radioactive iodipamide and subsequent opacification of the biliary tree on intravenous cholangiography.

RESULTS

The hepatic uptake curve of radioactivity can best be described by referring to Figure 1. Here the level of radioactivity represented by B is due to background radiation. Following the injection of radioactive iodipamide, there is a sharp rise in radioactivity and equilibrium is quickly reached at level E. The course that occurs from this point is the determining factor as to whether or not liver disease exists. Those patients without liver disease will show a definite upward trend, as indicated here. The results can be expressed as the per cent of increase or decrease of radioactivity from the equilibrium level by dividing the rise or fall (EC) by the equilibrium level (BE) and multiplying by 100. Those cases with borderline liver disease will have questionable concentration, whereas those with more marked liver disease will have a flat curve or actually show a decrease. The tracing in Figure 1 was made after a period of convalescence of proved hepatitis. An earlier tracing (Fig. 2) was made while the patient was in the hospital with hepatitis and shows a flat curve.

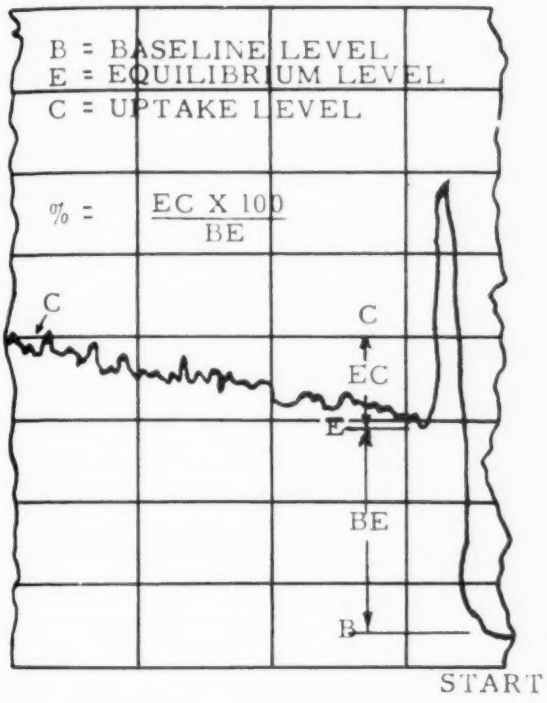

Fig. 1. The hepatic uptake of radioactive iodipamide in a patient after convalescence from hepatitis.

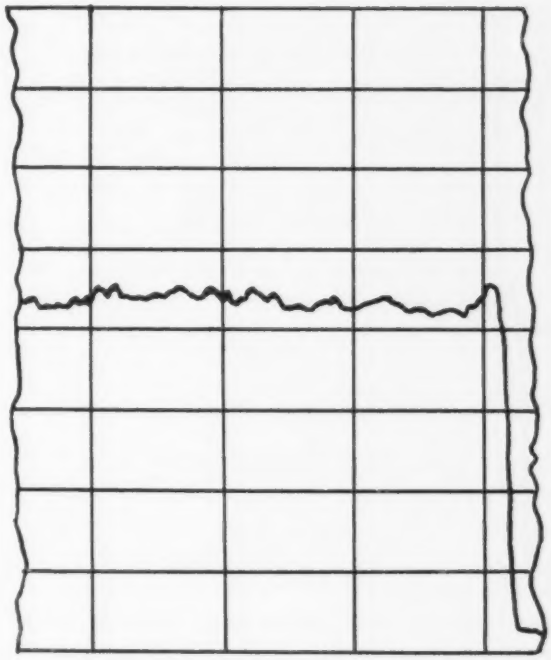

Fig. 2. The hepatic uptake of radioactive iodipamide in a patient with hepatitis (the same patient as in Figure 1).

A total of 36 patients with laboratory and clinical evidence of liver disease was included in this study. The average concentration of radioactivity above equilibrium levels was −3 per cent (±9). A total of 40 control patients was studied. The mean concentration of radioactivity by the liver above equilibrium levels in this group was +25 per cent (±12). Student's t value for this distribution is 4.4. The probability of this distribution being due to chance is less than 0.001.

The mean 3 hour urinary excretion for 10 controls was 2.5 per cent of the administered dose. The corresponding value for 15 patients with liver disease was 5.0 per cent. The 24 hour urinary excretion values were respectively 10.7 and 18.8 per cent. By use of the rank-sums test, the values for

TABLE I

RADIOACTIVE IODIPAMIDE DETERMINATIONS IN PATIENTS WITH AND WITHOUT LIVER DISEASE

Determination	Without Liver Disease		With Liver Disease		Probability of Chance Distribution
	Mean (per cent)	S.D.	Mean (per cent)	S.D.	
Hepatic Uptake	+25.0	±12.0	− 3.0	±9.0	0.001†
3 Hour Urine	+ 2.5	± 1.1	5.0	±3.0	0.10‡
24 Hour Urine	10.7	± 5.0	18.8	±8.6	0.001‡
3 Hour Blood*	9.2	± 5.8	13.0	±8.1	0.3‡
48 Hour Stools	32.0	±19.0	5.7	±6.7	0.01‡

* 1 liter of plasma.
† Determined by Student's test.
‡ Determined by rank-sums test.

3 hour excretion were shown to be significant at the 90 per cent level and for 24 hour excretion to the 99 per cent level.

The per cent of radioactivity remaining in the blood after 3 hours was calculated on the basis of one liter of plasma. The mean value for 19 controls was 9.2 (±5.8) per cent of administered dose as compared to 13.0 per cent (±8.1) for 21 patients with proved liver disease. These values were not significant when checked by the rank-sum test.

Stools of 6 patients without and 10 patients with liver disease were collected over a forty-eight hour period. The per cent of the administered radioactive iodipamide recovered in these collections was calculated. The mean values for the two groups respectively were 32 per cent (±19) and 5.7 per cent (±6.7). These results were significant to the 99 per cent level.

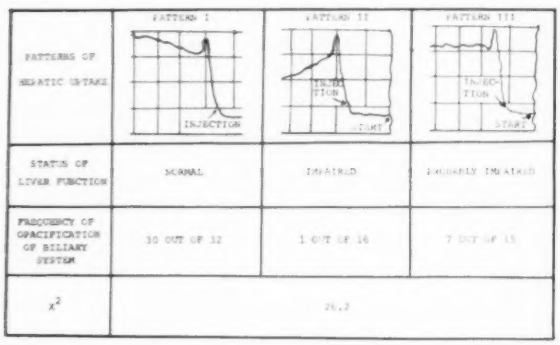

FIG. 3. The relationship between hepatic uptake patterns and frequency of opacification of the biliary system.

The various results given above are shown in Table I.

The hepatic uptake study also was performed on a total of 63 unselected patients for whom intravenous cholangiography had been requested. The technique was simplified in this group. A total of 2 ml. of iodipamide (1 ml. radioactive containing approximately 15 μc and 1 ml. test dose) was administered. The cardiac probe was not used.

The hepatic uptake curves can be divided into three basic patterns. The first of these shows definite hepatic concentration, the second shows a definite decrease in concentration in the liver, and the third is that in which the tracing is essentially flat (Fig. 3). Thirty-two patients showed Pattern I; in 30 of these the biliary tree was opacified on intravenous cholangiography. Pattern II was observed in 16 patients, and only 1 of these showed opacification of the biliary tract. Seven of 15 patients in the last category (Pattern III) showed opacification of the biliary tree on intravenous cholangiograms. Technical factors and habitus favoring good roentgenograms in this last group were important for biliary tract visualization. The chi-square value for the above distribution is 26.2, which is significant beyond the 99 per cent limits.

DISCUSSION

The course of the hepatic uptake curve after equilibrium is a balance between two parameters, namely, an increase of radio-

activity in the parenchyma and a decrease of radioactivity in the hepatic blood volume. A third factor, which is considered unlikely to affect the results because of the short time interval of the test, is the changing hepatic blood volume. Under these conditions curves with maximum or minimum points usually result. It is fortunate that the tracing obtained with this technique has a relatively flat maximum point and that a definite upward slope is obtained over a normal liver. The resultant curve is, therefore, easily interpreted. Although one can quantitate the results by calculating the per cent of increase or decrease in radioactivity from the equilibrium level, no complicated procedure is necessary for interpretation.

The uptake and excretion half times were determined by the method described by Lowenstein[5] for rose bengal. The uptake half time was approximately 30 minutes; the excretion half time, greater than 200 minutes. The long excretion time necessitates prolonged monitoring, which makes this procedure impractical for iodipamide.

It has been shown for radioactive rose bengal that, if the liver is monitored from the posterior aspect, contribution of radioactivity from the gallbladder will produce insignificant changes in the radioactivity monitored by the probe. Many of our patients were too ill or had too much ascites to lie in the prone position. For this reason we chose the supine position and monitored over the anterior aspect of the liver. The significant differences between the normal and abnormal groups justify the use of an anterior port. On a number of patients an additional probe was placed horizontally and the liver was monitored from a lateral aspect. These uptake curves were similar to those described in this paper.

We have previously shown that intravenous cholangiography can be of value in differentiating the entities producing the acute abdomen.[3] Unfortunately, approximately 40 per cent of patients presenting with an acute abdomen will fail to show opacification of the biliary tree and intravenous cholangiograms are indeterminate. This simple and rapid test, requiring little more time than the necessary sensitivity test for which it also serves, can be used to predetermine those patients in whom the biliary tree can be opacified. It should be pointed out, as indicated in an earlier paragraph of this presentation, that conventional laboratory studies likewise can be used. Unfortunately, the results of these tests are not always available when intravenous cholangiography is performed.

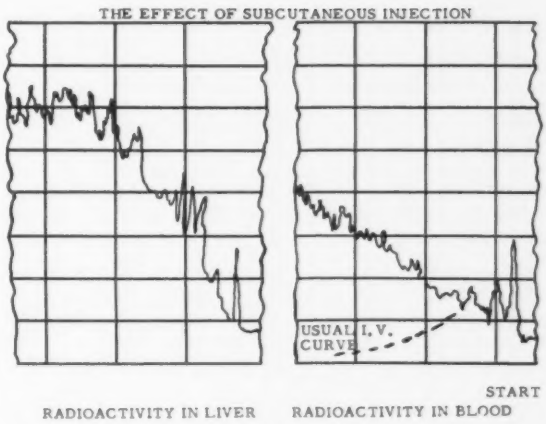

Fig. 4. Uptake curves after subcutaneous injection of radioactive iodipamide showing radioactivity in the liver (left) and radioactivity in the blood (right). (Reproduced by permission from *The Southern Medical Journal.*)

If a small quantity of iodipamide is infiltrated into the subcutaneous tissues, the hepatic tracing may be falsely read as showing good liver function. The curves after such an injection are shown in Figure 4. Usually the blood activity shows an exponential decay-type curve, as indicated by the dotted line in Figure 4. However, when significant amounts are given subcutaneously, the blood radioactivity slowly increases as the iodipamide is absorbed. In such cases the excellent concentration of radioactivity in the liver may indicate increasing radioactivity of the blood within the liver, not within the parenchyma. For this reason, the precordium was monitored with a second probe. However, this is not absolutely necessary since a sharp abrupt

rise on the hepatic tracing strongly favors an intravenous injection.

The number of cases included in the results of assaying biologic specimens is less than the number for hepatic uptakes. Some of the former were excluded because of contaminated or inadequately collected specimens.

Frommhold[1] indicated that the iodine was tightly bound to the iodipamide molecule and was not metabolized. Hence free iodine was not taken up by the thyroid gland. Monitoring of the thyroid gland subsequent to this test has failed to show appreciable radioactive uptake. However, in all probability, sufficient carrier iodipamide was present to block the uptake of I^{131} by the thyroid gland if any iodine were freed. Thyroid uptakes were performed on several patients without clinical evidence of thyroid disease and on whom hepatic uptakes of iodipamide had been done. The thyroid uptake values were in the myxedematous range, suggesting that sufficient iodine was released from iodipamide to block the thyroid gland.

Patients with congestive heart failure were excluded from this study because such patients failed to concentrate iodipamide. Further studies are in progress on the rate of reversibility of this defect following cardiac compensation. All 5 patients on whom multiple hepatic uptake tests have been performed have shown some increase in the uptake following cardiac compensation.

CONCLUSIONS

1. Statistically significant differences in the hepatic uptake of radioactive iodipamide were noted in patients with liver disease as compared to those without liver disease.

2. A definite upward slope of the normal hepatic uptake curve simplifies the interpretation of the test.

3. Nearly all patients showing a definite upward curve will subsequently show an opacified biliary tree on intravenous cholangiography.

4. Those patients who fail to show any concentration of radioactivity over the liver will rarely show subsequent opacification of the biliary tree on intravenous cholangiograms.

5. Approximately one-half of those patients in whom the hepatic uptake curve is flat or questionably upward in slope will show opacification of the biliary tree on intravenous cholangiography. In this group, habitus and technical factors for good roentgenography are of importance.

6. Significant differences between patients with and without liver disease were also noted in the excretion of radioactivity into urine and feces following the intravenous injection of radioactive iodipamide.

7. The clearance of radioactivity from the blood following the intravenous injection of radioactive iodipamide did not differ significantly in the two groups of patients.

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The American Journal of Roentgenology, Radium Therapy and Nuclear Medicine announces with deep regret the sudden death of Dr. Lawrence Reynolds on Thursday, August 17, 1961 in Detroit, Michigan.

Dr. Reynolds was Associate Editor of this Journal in 1928-1929 and its distinguished Editor since 1930 excepting the years of 1947 to 1949 during his tenure as President-Elect and President of the American Roentgen Ray Society.

DOSAGE LIMITATION IN THE COMBINED TREATMENT BY IRRADIATION AND SURGERY OF CARCINOMA OF THE UTERINE CERVIX

CONSIDERABLE initial enthusiasm has followed the revival of surgical techniques in the treatment of carcinoma of the uterine cervix. In the years since Wertheim's 1914 deploration: "It is a tragic fate being obliged to establish the fact that my life's work, the introduction of radical surgery in the treatment of carcinoma of the cervix has been unprofitable," radiotherapy has been acknowledged the more successful modality. Surgical recrudescence, foreshadowed in the development of the Taussig operation and the refinements of the Clark-Wertheim procedure and nurtured by better anesthesia, has been realized with the appearance of antibiotics and improved supportive care. Currently notable interest is evidenced in the feasibility of superimposing radical or quasi-radical operations upon high rad, large volume radiation dosages delivered to pelvic tissues.

Meaningful evaluation of normal pelvic visceral and supportive structure tolerances has been made by Wall *et al.*,[1] Frick *et al.*,[2] and Chau *et al.*[3] Their refreshing summations replace nonspecific roentgen administered tolerance gauging with details of time dose relationships, radium geometry and external radiation schedules. In the study of Wall *et al.*[1] severe complications appeared in 21 per cent of the patients receiving 4,000 r or more with external orthovoltage irradiation. Eight per cent developed major injury in those receiving 3,500 r to 4,000 r, and only a 2 per cent complication rate was observed in the 3,000 r to 3,500 r range. Doses in excess of 3,500 r added little to cure probability and greatly increased the risk of necrosis. Frick *et al.*[2] relate the difference in complication rates in those patients treated by radiotherapy to various dosage levels of external irradiation. Employing supervoltage techniques, injuries were significantly more common in patients given more than 4,000 r tumor dose. Dosages above 4,000 r to the pelvic wall have been abandoned by this group because of their hazardous consequences.

Chau *et al.*,[3] at the recent meeting of the American Radium Society, have discussed the complications appearing in 741 cases of cervical cancer. Patients receiving 4,000 r total pelvic irradiation exhibited freedom from persistent dysuria and bladder ulcer and almost no instances of proctitis or rectal ulcer were recorded. The incidence of sigmoiditis was practically nil at this dosage level. None of the patients in this group developed fistula or small bowel necrosis in the absence of an added surgical procedure. Chau *et al.* also concluded that higher dosage levels, provided no surgical procedure is added, are not conducive to excessive pelvic fibrosis or ureteral complications.

Several types of surgical procedures have been devised to meet various clinical situations. Brunschwig and Daniel[4] have described the most suitable operation when the rectum and bladder are uninvolved. "This is a radical panhysterectomy and pelvic node excision. The technique emphasizes complete node excision, including excision of the hypogastric artery and vein and denudation of the sciatic nerve roots in the posterior lateral pelvis." Complications peculiar to these surgical methods must be anticipated. Operative mortality has been effectively reduced; however, late postoperative complications remain the

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[2] Frick, H. C., II, Taylor, H. C., Jr., Guttmann, R. J., Jacox, H. W., and McKelway, W. P. Study of complications in surgical and radiation therapy of cancer of cervix. *Surg., Gynec. & Obst.*, 1960, *111*, 493–506.

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bête noire. Most important of these are ureterovaginal fistula, enteric fistula and bladder atony. Leg edema, wound infection, bowel stricture and adhesion produced intestinal obstruction are other adverse sequelae observed. In a group of early cases, cited by Frick *et al.*[2], undergoing radical hysterectomy and pelvic node dissection, major complications occurred in 18.4 per cent. Brunschwig and Daniel[4] performed this operation on 348 selected cases. Forty five urinary tract fistulae developed postoperatively. Many estimate that the incidence of ureterovaginal fistula alone will continue to occur in 10 per cent of the surgically treated cases.[2]

Combined aggressive surgical and radiotherapeutic measures expose the pelvic structures to the vicissitudes of both disciplines. Aside from the mathematical probability of increased complication rates, an additive factor appears inherent: blood supply already compromised by irradiation is further embarrassed by surgical intervention. Comparative studies in patients treated with radiation and those treated by combined approach reveal that the complications of both methods are potentiated when certain time dose radiation thresholds are exceeded. Frick *et al.*[2] found in three series of patients receiving at least 4,000 r that without added surgery the major complication rate was 5 per cent; with lymphadenectomy, the major morbidity incidence rose to 36 per cent, and in those subjected to radical hysterectomyand lymphadenectomy complications appeared in 20 per cent. In a parallel analysis in which patients received less than 4,000 r in the presence of superimposed surgery, complications were decreased by more than one third.

In the series of Chau *et al.*[3] small bowel necrosis, sigmoiditis and fistulae developed in 21.5 per cent of patients treated by radiation therapy and lymphadenectomy. Twenty three per cent in the group which had hysterectomy or exenteration with lymphadenectomy plus radiation therapy developed undesirable sequelae. They concluded that 4,000 rad whole pelvis irradiation is a safe technique even if lymphadenectomy and/or hysterectomy are added.

Gray and co-workers[5] regard the development of lymphocysts, occurring in 17 per cent of their cases, as a major problem in postirradiation lymphadenectomy. A lymphocyst is a collection of serous fluid which develops retroperitoneally in the denuded iliac vessel region. It appears that there is a correlation with the amount of tissue removed, and that a definitely higher number of lymphocysts is observed in persons receiving preliminary irradiation. This high incidence and the frequency of required secondary surgical procedures with prolonged convalescence create a prohibitive morbidity rate. Chau *et al.*[3] comment that these cysts can result in ureteral obstruction and effect vascular occlusion.

The prospect of increasing survival rates in carcinoma of the cervix is a constant lure to surgeons and radiotherapists. Some injuries are acceptable. Yet, a point of diminishing return is reached where complication yield precludes further treatment. Brunschwig and Daniel[4] have remarked that "Modern surgical attack in cancer of the cervix should for the present be confined to institutions with adequate equipment, whose personnel have the requisite surgical skill." Leucutia[6] in the Caldwell Lecture of 1960 reiterated, "The effect of reintroduction of radical surgery upon the over-all results appears to be statistically small and needs further investigative evaluation." Thus, the efficacy of treating carcinoma of the cervix with combined irradiation and radical surgery has not as yet emerged from the phase of experimental appraisal. However, when such a

[4] Brunschwig, A., and Daniel, W. Surgical treatment of cancer of cervix uteri. *Am. J. Obst. & Gynec.*, 1958, *75*, 875–881.

[5] Gray, M. J., Gusberg, S. G., and Guttmann, R. Pelvic lymph node dissection following radiotherapy. *Am. J. Obst. & Gynec.*, 1958, *76*, 629–633.

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combined approach is contemplated, supplementary supervoltage external irradiation should not exceed 4,000 rads to the pelvic tissues. This is more than experimental data or work in progress; it is accumulated clinical fact. The clarion for higher survival rates from ever increasing radiation dosages and extensive surgery is muted by normal tissue intolerance.

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THE REGISTRY OF RADIOLOGIC PATHOLOGY

The American Registry of Pathology of the Armed Forces Institute of Pathology

IN 1947 the American College of Radiology, the American Roentgen Ray Society, and the Radiologic Society of North America jointly sponsored a Registry of Radiologic Pathology within the framework of the American Registry of Pathology. Outside of the academic family of medical schools, however, it would appear that relatively few physicians are aware of the purpose of the American Registry of Pathology, and that even fewer practicing radiologists know of the Registry of Radiologic Pathology. Perhaps the American Registry of Pathology can be of greatest service to those physicians outside the immediate academic family of medical schools. Since this group is relatively uninformed about the Registry, a brief historic background is indicated.

In 1862, nearly 100 years ago, the Armed Forces Institute of Pathology was founded. Originally known as the Army Medical Museum, it consisted of three dried and varnished specimens resting on a small shelf above the inkstand on the curator's desk. From this modest beginning, the Armed Forces Institute of Pathology today houses more than one million accessions, comprised of surgical biopsy specimens, complete autopsy data and specimens, and allied pathology material all filed for teaching, research and posterity. In 1946 the Army Medical Museum was renamed the Army Institute of Pathology. In 1949, following the unification of the armed services, the present designation, the Armed Forces Institute of Pathology of the Department of Defense, was adopted.

The Armed Forces Institute of Pathology has four major components: the department of pathology, the medical illustration service, the American registry of pathology, and the medical museum. Unknown to many civilian physicians is the consultation service for the diagnosis of pathologic tissue. The consultation service, established primarily for what is now the Department of Defense and other federal agencies, is also available to any civilian pathologist or other physician in need of a board of arbitration to help him arrive at a final pathologic diagnosis. It is obvious that such a service is probably of greatest value to those civilian physicians practicing outside of large academic institutions. Another function of the department of pathology is to prepare, or procure and duplicate, pathologic, photographic, and other educational material. This material is donated or loaned to other Federal medical services, museums, medical schools, scientific institutions, and to qualified persons connected with the medical, dental, or veterinary professions. Many civilian residents in the surgical and pathology specialties have availed themselves of these loan slides before taking their specialty board examinations.

The first of the American Registries of Pathology had its inception in 1922. In that year, Major George Russell Callender, curator of the Army Medical Museum, with the cooperation of the American Academy of Ophthalmology, organized a registry of ophthalmic pathology, where pathology relative to the eye could be collected and cases followed for study and research. In 1925 the second of the registries was organized, under the sponsorship of the American Association of Pathologists and Bacteriologists, to attempt to classify lymphatic tumors. Today there are 22 such registries all housed within the framework of the Armed Forces Institute of Pathology under the auspices of the National Research Council and each, except endocrine pathology, sponsored by a national medical, dental, or veterinary society. It is indeed fortunate that the farsighted thinking

of Dr. Callender has led to the housing in one repository of this tremendous wealth of pathologic material.

Criticism of the housing of the registries within an agency of the United States Government has been voiced by many academicians around the country. This criticism would sometimes appear to bear the implication of special pleading, since some of these specialists argue for the acquisition of a specific registry within their own academic institution. Obviously this treasury of information could easily be dispersed throughout dozens of deserving institutions—as could, indeed, the Library of Congress or the Smithsonian Institution, —thereby destroying its very reason for existence as a great corpus of information available to the United States Government and to all civilian physicians, dentists, and veterinarians.

In this period of history, when public funds are necessarily being directed to potentially destructive purposes in the interests of the nation's preservation, it is gratifying to see this great repository of scientific knowledge, built with public funds to amass knowledge for the alleviation of suffering, and to cure disease in generations to come.

In 1947 the fifteenth registry was organized, the Registry of Radiologic Pathology. At its inception, as is true of many new undertakings, there was little organization or purpose. However, in the intervening fourteen years, this registry has become one of the truly great study centers for correlation of disturbed morphology viewed radiologically and the gross and microscopic pathology of the tissues. There are now some 12,000 cases in this registry complete with history, reproductions of the roentgenograms, photographs of the gross pathology, and histologic sections.

The splendid organization of this registry is a labor of love of one man. Early in the life of the registry, the sponsoring societies realized that a consultant serving for one week each quarter was not enough, and that a part-time director in residence was necessary. Fortunately the right man was found. Colonel William L. Thompson, MC (Ret.), took on what was regarded as a part-time job and offered his services without remuneration. But the Colonel was not content to do a part-time job. Daily Colonel Thompson is at the Institute doing didactic teaching for four hours and spending the other four in accessioning new material and organizing the old. Not only does the Colonel impart a wealth of knowledge to the residents and fellows, but he succeeds in bestowing a spark of enthusiasm and joy for the practice of radiology to each man in turn. Nowhere, in the writer's opinion, is there so great an opportunity for a man nearing the end of his residency to pull all the loose ends together, and to correlate the various radiologic patterns of disturbed morphology in terms of gross pathology.

Dedicated men with Colonel Thompson's zeal and ability to teach are not common. It is hoped that the sponsoring organizations will actively look to the future for an able successor and a much more adequate remuneration than has been Colonel Thompson's lot in this important post.

In conclusion, the need for continually enriching the registry with new material is obvious. Such a registry should have within it the best that each teaching institution throughout the country possesses, both the esoteric and the routine. There is a great reluctance on the part of some specialists in various academic institutions to send cases for accession, on the grounds that the cases are lost for local reporting, and are eventually reported in the literature by the Armed Forces Institute of Pathology. This, of course, raises the question of whether medical writing should serve for personal aggrandizement, when the piecemeal publication of isolated cases obviously is less meaningful than comprehensive reporting by the Institute. For example, the study and reporting of pulmonary alveolar proteinosis might never

have been possible in a single institution. The Armed Forces Institute of Pathology, on its part, should be scrupulous in making full acknowledgment of the provenance of material it publishes.

It is hoped that more directors of departments of radiology throughout the country will avail themselves of the opportunity of sending their older residents to the Armed Forces Institute of Pathology for their pathology, and that more material, both esoteric and routine, will find its way to the registries.

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BOOKS RECEIVED

Books sent for review are acknowledged under: Books Received. This must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interest of our readers as space permits.

BOOKS RECEIVED

The Use of Isotopes in Haematology. By L. G. Lajtha, M.D., D.Phil., Member External Staff Medical Research Council, Radiobiology Laboratory, Department of Radiotherapy, Churchill Hospital, Oxford, England. Cloth. Price, $4.75. Pp. 83, with 27 illustrations. Charles C Thomas, Publisher, 301–327 East Lawrence Avenue, Springfield, Ill., 1961.

Onsets, Completions, and Spans of the Osseous Stage of Development in Representative Bone Growth Centers of the Extremities. By S. Idell Pyle, Harold C. Stuart, Joan Cornoni, and Robert B. Reed, Harvard University School of Public Health, 55 Shattuck Street, Boston 15, Massachusetts. Paper. Price, $3.25. Pp. 125, with 46 illustrations and 10 tables. Published by Child Development Publications of the Society for Research in Child Development, Inc., Purdue University, Lafayette, Indiana, 1961.

Traité de Technique Chirurgicale. Vol. III. By B. Fey, P. Mocquot, S. Oberlin, J. Quénu, P. Truffert, M. David, M. Iselin, R. Dossot, R. Dubau, Ch. Dubost, J.-J. Galey, Y. Longuet, J. Loygue, J. Mathey, F. Palmer, J. Perrotin, J. Rudler, G. Thomeret, and J. Varangot. Cloth. Pp. 698, with 532 illustrations. Masson et Cie, Éditeurs 120 Boulevard Saint-Germain, Paris (6e), France, 1961.

Acta Orthopaedica Scandinavica, Supplementum No. 49. Comparative Value of Electromyographic, Myelographic and Clinical-Neurological Examinations in Diagnosis of Lumbar Root Compression Syndrome. By Bertil Knutsson. Paper. Pp. 135, with 30 tables. Ejnar Munksgaard, Copenhagen, 1961.

Acta Orthopaedica Scandinavica, Supplementum No. 51. Nervous and Vascular Influence on Longitudinal Growth of Bone; An Experimental Study on Rabbits. By Henry Troupp. Paper. Pp. 78, with 42 illustrations. Ejnar Munksgaard, Copenhagen, 1961.

Proceedings of the Fourth National Cancer Conference. Sponsored by American Cancer Society, Inc. and National Cancer Institute, U. S. Public Health Service. Cloth. Price, $9.00. Pp. 774, with numerous illustrations. J. B. Lippincott Company, 227–231 S. Sixth Street, Philadelphia, Pa., 1961.

Acta Orthopaedica Scandinavica, Supplementum No. 44A. Comparison Between Biological Assays and the Ferroxyl Test for Studying Corrosion of Experimental Metal Implants. By Hans Emnéus. Paper. Pp. 15, with 5 figures and 2 tables. Ejnar Munksgaard, Copenhagen, Denmark, 1960.

The Scandinavian Journal of Clinical & Laboratory Investigation. Vol. 12—Supplementum 50. Rational Use of Antiobiotics in Hospitals; Studies on Laboratory Methods and Discussion of the Biological Basis for Their Clinical Application. By Hans Ericsson. Paper Pp. 59. Stockholm, Sweden, 1960.

The Scandinavian Journal of Clinical & Laboratory Investigation. Vol. 12—Supplementum 51. The Adhesiveness of Human Blood Platelets In Vitro. By Arvid John Hellem. Paper. Pp. 117. Islo, 1960.

The Scandinavian Journal of Clinical & Laboratory Investigation. Vol. 12—Supplementum 52. Polyunsaturated Fatty Acids in Man; Serum, Cutaneous and Subcutaneous Levels in Individuals with Normal and Elevated Serum Lipids. By Per Björntorp. Paper. Pp. 147. Oslo, 1960.

The Scandinavian Journal & Laboratory Investigation. Vol. 12—Supplementum 53. The Effect of EDTA on Human Fibrinogen and Its Significance for the Coagulation of Fibrinogen with Thrombin. By Hans Christian Godal. Paper. Pp. 20. Oslo, 1960.

The Scandinavian Journal of Clinical & Laboratory Investigation. Vol. 12—Supplementum 54. The Elimination of Uric Acid in Man; Studied by Means of C^{14}-labeled Uric Acid; Uricolysis, By Leif Bøge Sørensen. Paper. Pp. 214. Oslo, 1960.

SOCIETY PROCEEDINGS

MEETINGS OF RADIOLOGICAL SOCIETIES*

United States of America

American Roentgen Ray Society
Secretary, Dr. C. Allen Good, Mayo Clinic, Rochester, Minn. Annual meeting: Deauville Hotel, Miami Beach, Fla., Sept. 26–29, 1961.

American Radium Society
Secretary, Dr. Charles G. Stetson, 350 Engle Street, Englewood, N. J. Annual meeting: Waldorf-Astoria Hotel, New York, N. Y., April 1–4, 1962.

Radiological Society of North America
Secretary, Maurice Doyle Frazer, 1744 South Fifty-eighth St., Lincoln, Neb.
Treasurer, Dwight Vincent Needham, 713 E. Genessee St., Syracuse, N. Y. Annual Meeting: Palmer House, Chicago, Ill., Nov. 26–Dec. 1, 1961.

American College of Radiology
Executive Director, William C. Stronach, 20 N. Wacker Drive, Chicago 6, Illinois. Annual meeting: Roosevelt Hotel, New York, N. Y. Feb. 7–10, 1962.

Section on Radiology, American Medical Association
Secretary, Dr. Clyde A. Stevenson, Sacred Heart Hospital, West 101 Eighth Ave., Spokane 4, Wash. Annual meeting: Chicago, Ill., June 11–15, 1962.

American Board of Radiology
Secretary, Dr. H. Dabney Kerr. Correspondence should be directed to Kahler Hotel Building, Rochester, Minn. The Fall 1961 examination will be held at the Shoreham Hotel, Washington, D. C., December 4–7, inclusive; the deadline for filing applications was July 1, 1961. A Special Examination in Nuclear Medicine will be offered if there are sufficient applications.

American Association of Physicists in Medicine
Secretary-Treasurer, Charles S. Simons, University of Michigan Hospital, Ann Arbor, Mich. Annual meeting to be announced.

Tenth International Congress of Radiology
Secretary-General, Dr. Carleton B. Peirce, Royal Victoria Hospital, Montreal 2, Quebec, Canada. Meets in Montreal, Aug. 26–Sept. 1, 1962.

Eighth Inter-American Congress of Radiology
Counselor for the United States, Dr. J. A. del Regato, Penrose Cancer Hospital, 2200 North Cascade Avenue, Colorado Springs, Colorado. Meeting to be announced.

Alabama Radiological Society
Secretary, Dr. J. A. Meadows, Jr., Medical Arts Bldg., Birmingham 5, Ala. Meets time and place Alabama State Medical Association.

American Nuclear Society
Executive-Secretary, Octave J. Du Temple, 86 E. Randolph St., Chicago, Ill.

Arizona Radiological Society
Secretary, Dr. Don E. Matthieson, 926 East McDowell Rd., Phoenix, Ariz. Two regular meetings a year. Annual meeting at time and place of State Medical Association and interim meeting six months later.

Arkansas Radiological Society
Secretary, Dr. Charles W. Anderson, 1108½ Poplar, Pine Bluff, Ark. Meets every three months and also at time and place of State Medical Association.

Association of University Radiologists
Secretary, Dr. Herbert M. Stauffer, Temple University Medical Center, Philadelphia 40, Pa. Annual Meeting: University of Indiana, Indianapolis, Ind., May 19–20, 1962.

Atlanta Radiological Society
Secretary, Dr. Wilson T. Edenfield, 35 Linden Ave., N.E., Atlanta 8, Ga. Meets monthly, except during three summer months, on second Friday evening.

Blockly Radiological Society
Secretary, Dr. Samuel Finkelman, 101 S. Twentieth St., Philadelphia, Pa.

Brooklyn Radiological Society
Secretary, Dr. Joseph Arcomano, 168 Clinton St., Brooklyn 1, N. Y. Meets first Thursday of each month October through May.

Buffalo Radiological Society
Secretary, Dr. R. Joseph Naples, 106 Morgan Parkway, Williamsville 21, N. Y. Meets second Monday evening each month, October to May inclusive.

Central New York Radiological Society
Secretary, Dr. Joseph A. Head, 150 Marshall St., Syracuse, N. Y. Meets first Monday each month October through May.

Central Ohio Radiological Society
Secretary, Dr. Robert L. Freidman, Grant Hospital, Columbus, Ohio. Meets at 6:30 P.M. on second Thursday of October, November, January, March and May at Fort Hayes Hotel, Columbus, Ohio.

Central Society of Nuclear Medicine
Secretary, Dr. Robert S. Landauer, Radiation Center Building, 1903 West Harrison St., Chicago 12, Ill.

Chicago Roentgen Society
Secretary, Dr. William F. Hutson, 5145 N. California Ave., Chicago, Ill. Meets second Thursday of each month, October to April except December at the Sheraton Hotel at 8:00 P.M.

Cleveland Radiological Society
Secretary, Dr. Norman E. Berman, 14404 S. Park Blvd., Shaker Hgts. 20, Ohio. Meetings at 7:00 P.M. on fourth Monday of each month from October to April at Tudor Arms Hotel.

Colorado Radiological Society
Secretary, Dr. Seward Imes, 1845 High St., Denver, Colo. Meets third Friday of each month at Denver Athletic Club from September through May.

Connecticut Valley Radiologic Society
Secretary, Dr. James L. Krieger, 85 Jefferson St., Hartford, Conn. Meets first Friday in February and April.

Dallas-Fort Worth Radiological Society
Secretary, Dr. F. J. Bonte, 5201 Harry Hines Blvd., Dallas 35, Texas. Meets monthly, third Monday, at Greater Fort Worth International Airport at 6:30 P.M.

Detroit Roentgen Ray and Radium Society
Secretary, Dr. Kenneth L. Krabbenhoft, Harper Hospital, Detroit 1, Mich. Meets monthly first Thursday, October through May, at David Whitney House, 1010 Antietam, at 6:30 P.M.

East Bay Roentgen Society
Secretary, Dr. Dan Tucker, 434 30th St., Oakland 9, Calif. Meets first Thursday each month at Peralta Hospital, Oakland.

East Tennessee Radiological Society
Secretary, Dr. J. Marsh Frere, Jr., 205 Medica Arts Building, Knoxville, Tenn. Meets in January and September.

Eastern Conference of Radiology
Secretary, Arrangements Committee, Dr. Philip Myers, Baltimore City Hospital, Baltimore 24, Md. Annual meeting to be announced.

Eastern Radiological Society
Secretary, Dr. James F. Martin, North Carolina Baptist Hospital, Winston-Salem, N. C. Meets at Mid Pines Club, Southern Pines, N. C., April 29–May 2, 1962.

*** Secretaries of societies are requested to send timely information promptly to the Editor.**

Florida Radiological Society
Secretary, Dr. Richard D. Shapiro, 1680 Meridian Ave., Miami Beach, Fla. Meets twice annually, in the spring with the annual State Society Meeting, and in the fall.

Florida West Coast Radiological Society
Secretary-Treasurer, Dr. Joseph C. Rush, 1800 Druid Rd., Clearwater, Fla.

Georgia Radiological Society
Secretary, Dr. George W. Brown, Griffin, Ga. Meets in spring and fall with Annual State Society Meeting.

Greater Miami Radiological Society
Secretary, Dr. Carl E. Balli, 907–8 Huntington Medical Building, Miami 32, Fla. Meets monthly third Wednesday at 8:00 P.M. at Jackson Memorial Hospital, Miami, Fla.

Greater St. Louis Society of Radiologists
Secretary, Dr. William E. Powers, St. Louis, Mo.

Houston Radiological Society
Secretary, Dr. John Douglas Reeve, Texas Medical Center Library, Jesse H. Jones Library Bldg., Houston 25, Texas. Meets last Monday each month, Seminar Room, Doctors' Club of Houston.

Idaho State Radiological Society
Secretary, Dr. George H. Harris, Bannock Memorial Hospital, Pocatello, Idaho. Meets in the Spring and Fall.

Illinois Radiological Society
Secretary, Dr. George A. Miller, Carle Hospital Clinic, Urbana, Ill. Meets in spring and fall.

Indiana Roentgen Society, Inc.
Secretary, Dr. David E. Wheeler, 1500 North Ritter, Indianapolis, Ind. Meets first Sunday in May and during fall meeting of Indiana State Medical Association.

Iowa Radiological Society
Secretary, Dr. L. L. Maher, 1419 Woodland Ave., Des Moines, Iowa. Luncheon and business meeting during annual session of Iowa State Medical Society. The scientific section is held in the autumn.

Kansas Radiological Society
Secretary, Dr. Roger K. Wallace, Riley County Hospital, Manhattan, Kansas. Meets in spring with State Medical Society, and in winter on call.

Kentucky Radiological Society
Secretary, Dr. Lawrence A. Davis, 226 East Chestnut St., Louisville, Ky. Meets monthly on second Friday at Seelbach Hotel, Louisville.

Kings County Radiological Society
Secretary, Dr. Abraham Berens, 1917 Bedford Ave., Brooklyn 25, N. Y. Meets Kings County Med. Soc. Bldg. monthly on fourth Thursday, October to May, 8:45 P.M.

Los Angeles Radiological Society
Secretary, Dr. Saul Heiser, Los Angeles, Calif. Meets second Wednesday of month in September, November, January, March and June at Los Angeles County Medical Association Building, Los Angeles.

Maine Radiological Society
Secretary, Dr. Albert A. Poulin, Thayer Hospital, Waterville, Maine. Meets in June, September, December and April.

Maryland Radiological Society
Secretary, Dr. Nathan B. Hyman, 1805 Eutaw Place, Baltimore 17, Md.

Memphis Roentgen Society
Secretary, Dr. Irving K. Ettman, Kennedy V.A. Hospital, Department of Radiology, Memphis 15, Tenn. Meets first Monday of each month at John Gaston Hospital.

Miami Valley Radiological Society
Secretary, Dr. William D. Roberts, 2197 Los Arrow Dr., Dayton 9, Ohio. Meets second Friday of fall and winter months.

Mid-Hudson Radiological Society
Secretary, Dr. Joseph Sorrentino, St. Francis Hospital, Poughkeepsie, N. Y. Meets 8:30 P.M., fourth Wednesday each month, September to May.

Milwaukee Roentgen Ray Society
Secretary, Dr. Abraham Marck, Mayfair Professional Bldg., Milwaukee 13, Wis. Meets monthly on fourth Monday, October through May, at University Club.

Minnesota Radiological Society
Secretary, Dr. Donald H. Peterson, 853 Medical Arts Bldg., Minneapolis 2, Minn. Meets three times annually, in fall, winter and spring.

Mississippi Radiological Society
Secretary, Dr. Jack K. Goodrich, University Medical Center, Jackson, Miss. Meets third Thursday of each month at Hotel Edwards, Jackson, at 6:00 P.M.

Montana Radiological Society
Secretary, Dr. J. K. Boughn, 35 11th Ave., Helena, Montana. Meets at least once a year.

Nassau Radiological Society
Secretary, Dr. Robert Tugendhaft, 100 Nowbridge Rd., Hicksville, N. Y. Meets second Tuesday of the month in February, April, June, October and December.

Nebraska Radiological Society
Secretary, Dr. Ronald E. Waggener, The Radiologic Center, Nebraska Methodist Hospital, Omaha 31, Nebraska. Meets third Wednesday of each month at 6 P.M. in Omaha or Lincoln.

New England Roentgen Ray Society
Secretary, Dr. Robert E. Wise, 605 Commonwealth Ave., Boston 15, Mass. Meets third Friday of each month, October through April at The Longwood Towers, Brookline, Mass.

New Hampshire Roentgen Ray Society
Secretary, Dr. Paul Y. Hasserjian, 1470 Elm St., Manchester, N. H. Meets four to six times yearly

New York Roentgen Society
Secretary, Dr. Bernard Wolf, Mt. Sinai Hospital, New York, N. Y. Meets monthly on third Monday, New York Academy of Medicine at 4:30 P.M.

North Carolina Radiological Society
Secretary, Dr. A. B. Croom, 624 Quaker Lane, High Point, N. C. Meets in the spring and fall each year.

North Dakota Radiological Society
Secretary, Dr. R. F. Raasch, Post Office Box 990, Dickinson, North Dakota. Meets at time of State Medical Association meeting. Other meetings arranged on call of the President.

North Florida Radiological Society
Secretary, Dr. Charles H. Newell, 800 Miami Road, Jacksonville 7, Fla. Meets quarterly in March, June, September and December.

Northeastern New York Radiological Society
Secretary, Dr. Lester I. Citrin, St. Mary's Hospital, Troy, N. Y. Meets in Albany area on second Wednesday of October, November, March and April.

Northern California Radiological Society
Secretary, Dr. Rob H. Kirkpatrick, 1219 28th St., Sacramento, Calif. Meets at dinner last Monday of each month, September to June.

Northwestern Ohio Radiological Society
Secretary, Dr. George Asahina, 421 Michigan St., Toledo, Ohio.

Ohio State Radiological Society
Secretary, Dr. Paul D. Meyer, 125 S. Grant Ave., Columbus, Ohio. Annual meeting to be announced.

Oklahoma State Radiological Society
Secretary, Dr. Simon Pollack, Utica Square Medical Center, Tulsa, Okla. Meets in January, May and October

Oregon Radiological Society
Secretary, Dr. George R. Satterwhite, Willamette Falls Community Hospital, 15th and Division, Oregon City, Ore. Meets monthly from October to June on the sec-

ond Wednesday of each month at 8:00 P.M. at the University Club.

ORLEANS PARISH RADIOLOGICAL SOCIETY
Secretary, Dr. Joseph V. Schlosser, Charity Hospital, New Orleans 13, La. Meets second Tuesday of each month.

PACIFIC NORTHWEST RADIOLOGICAL SOCIETY
Secretary, Dr. John N. Burkey, 555 Dental Bldg., Seattle, Wash. Annual meeting: Seattle, Washington.

PACIFIC ROENTGEN SOCIETY
Secretary, Dr. L. H. Garland, 450 Sutter St., San Francisco 8, Calif. Meets annually during meeting of California Medical Association.

PENNSYLVANIA RADIOLOGICAL SOCIETY
Secretary, Dr. Frederick R. Gilmore, Clearfield Hospital, Clearfield, Pa. Annual meeting: Pocono Manor Inn, May 25–26, 1962.

PHILADELPHIA ROENTGEN RAY SOCIETY
Secretary, Dr. Robert B. Funch, Department of Radiology, Germantown Hospital, Philadelphia 44, Pa. Meets first Thursday of each month, at 5 P.M., from October to May in Thompson Hall, College of Physicians.

PITTSBURGH ROENTGEN SOCIETY
Secretary, Dr. Ross H. Smith, St. Margaret Memorial Hospital, Forty-Sixth St., Pittsburgh 1, Pa. Meets second Wednesday of month, October through June at Park Schenely Restaurant.

RADIOLOGICAL SECTION, BALTIMORE MEDICAL SOCIETY
Secretary, Dr. James K. V. Willson, 1100 N. Charles St., Baltimore 1, Md. Meets third Tuesday each month, September to May, inclusive.

RADIOLOGICAL SOCIETY OF GREATER CINCINNATI
Secretary, Dr. Donald Janny, Cincinnati, Ohio. Meets monthly from September to May on first Monday of each month at 7:30 P.M. at the Cincinnati General Hospital.

RADIOLOGICAL SOCIETY OF HAWAII
Secretary, Dr. G. J. Liese, Queen's Hospital, Honolulu, Hawaii. Meets third Monday of each month at 7:30 P.M.

RADIOLOGICAL SOCIETY OF GREATER KANSAS CITY
Secretary, Dr. J. Stewart Whitmore, 1010 Rialto Bldg., Kansas City, Mo. Meets last Friday of each month.

RADIOLOGICAL SOCIETY OF KANSAS CITY
Secretary, Dr. Arthur B. Smith, 800 Argyle Bldg., Kansas City, Mo. Meets third Thursday of each month.

RADIOLOGICAL SOCIETY OF LOUISIANA
Secretary, Dr. Robyn Hardy, 4324 Magnolia St., New Orleans 15, La. Meets annually during Louisiana State Medical Society meeting.

RADIOLOGICAL SOCIETY OF NEW JERSEY
Secretary, Dr. George H. Burke, 601 Grand Ave., Asbury, Park, N. J. Meets at Atlantic City at time of State Medical Society meeting and in November in Newark, N. J.

RADIOLOGICAL SOCIETY OF THE STATE OF NEW YORK
Secretary-Treasurer, Dr. John W. Colgan, 273 Hollywood Ave., Rochester 18, N. Y. Annual meeting to be announced.

RADIOLOGICAL SOCIETY OF SOUTH DAKOTA
Secretary-Treasurer, Dr. Donald J. Peik, 303 S. Minnesota Ave., Sioux Falls, S. D.

RADIOLOGICAL SOCIETY OF SOUTHERN CALIFORNIA
Secretary, Dr. Joseph F. Linsman, 436 N. Roxbury Dr., Beverly Hills, Calif.

REDWOOD EMPIRE RADIOLOGICAL SOCIETY
Secretary, Dr. Lee E. Titus, 164 W. Napa St., Sonoma, Calif. Meets second Monday every other month.

RICHMOND COUNTY RADIOLOGICAL SOCIETY
Secretary, Dr. W. F. Hamilton, Jr., University Hospital, Augusta, Ga. Meets first Thursday of each month at various hospitals.

ROCHESTER ROENTGEN RAY SOCIETY, ROCHESTER, N. Y.
Secretary, Dr. Robert H. Greenlaw, 260 Crittenden Blvd., Rochester 20, N. Y. Meets at 8:15 P.M. on the last Monday of each month, September through May, at Strong Memorial Hospital.

ROCKY MOUNTAIN RADIOLOGICAL SOCIETY
Secretary, Dr. John H. Freed, 4200 East Ninth Ave., Denver 20, Colo. Annual meeting to be announced.

SAN ANTONIO-MILITARY RADIOLOGICAL SOCIETY
Secretary, Dr. Hugo F. Elmendorf, Jr., 730 Medical Arts Bldg., San Antonio 5, Texas. Meets third Wednesday each month in Fort Sam Houston Officer's Club at 6:30 P.M.

SAN DIEGO RADIOLOGICAL SOCIETY
Secretary, Dr. Stanley A. Moore, 2466 First Ave., San Diego 1, Calif. Meets first Wednesday of each month at the University Club.

SAN FRANCISCO RADIOLOGICAL SOCIETY
Secretary, Dr. M. A. Sisson, 450 Sutter St., San Francisco 8, Calif. Meets quarterly at the San Francisco Medical Society, 250 Masonic Ave., San Francisco 18, Calif.

SECTION ON RADIOLOGY, CALIFORNIA MEDICAL ASSOCIATION
Secretary, Dr. William H. Graham, 630 East Santa Clara St., San Jose, Calif.

SECTION ON RADIOLOGY, CONNECTICUT STATE MEDICAL SOCIETY
Secretary, Dr. Wayne P. Whitcomb, Hospital of St. Raphael, New Haven, Conn. Meetings are held bimonthly.

SECTION ON RADIOLOGY, MEDICAL SOCIETY OF THE DISTRICT OF COLUMBIA
Secretary, Dr. William E. Sheely, 1746 K St., N.W., Washington 6, D. C. Meets at Medical Society Library, third Wednesday of January, March, May and October at 8:00 P.M.

SECTION ON RADIOLOGY, ILLINOIS STATE MEDICAL SOCIETY
Secretary, Dr. William Meszaros, 1825 W. Harrison St., Chicago, Ill.

SECTION ON RADIOLOGY, SOUTHERN MEDICAL ASSOCIATION
Secretary, Dr. Seymour Ochsner, Ochsner Clinic, 3503 Prytania St., New Orleans 15, La. Annual meeting to be announced.

SHREVEPORT RADIOLOGICAL CLUB
Secretary, W. R. Harwell, 608 Travis St., Shreveport, La. Meets monthly on third Wednesday, at 7:30 P.M., September to May inclusive.

SOCIETY FOR PEDIATRIC RADIOLOGY
Secretary, Dr. Richard G. Lester, 412 Union St., S.E., Minneapolis 14, Minn. Annual meeting: Deauville Hotel, Miami Beach, Fla., Sept. 25, 1961.

SOCIETY OF NUCLEAR MEDICINE
Secretary, Dr. Robert W. Lackey, 452 Metropolitan Bldg., Denver 2, Colo. *Administrator*, Samuel N. Turiel, 430 N. Michigan Ave., Chicago 11, Ill. Annual meeting: Baker Hotel, Dallas, Texas, June 27–30, 1962.

SOUTH BAY RADIOLOGICAL SOCIETY
Secretary, Dr. Stanford B. Rossiter, 1111 University Dr., Menlo Park, Calif. Meets second Wednesday of each month.

SOUTH CAROLINA RADIOLOGICAL SOCIETY
Secretary, Dr. George W. Brunson, 1406 Gregg St., Columbia, S. C. Annual meeting (primarily business) in conjunction with the South Carolina Medical Association meeting in May. Annual fall scientific meeting at time and place designated by the president.

SOUTHERN RADIOLOGICAL CONFERENCE
Secretary, Dr. Marshall Eskridge, Mobile Infirmary, P.O. Box 4097, Mobile, Ala.

SOUTHWESTERN RADIOLOGICAL SOCIETY
Secretary, Dr. Ralph S. Clayton, 1501 Arizona, Bldg. 2-A, El Paso, Texas. Meets second Tuesday of each month.

TENNESSEE RADIOLOGICAL SOCIETY
Secretary, Dr. B. M. Brady, St. Joseph Hospital, Memphis, Tenn. Meets annually at the time and place of the Tennessee State Medical Association meeting.

TEXAS RADIOLOGICAL SOCIETY
Secretary, Dr. R. P. O'Bannon, 402 Professional Bldg., 1216 Pennsylvania Ave., Fort Worth 4, Texas. Annual meeting: Austin, Texas, Jan. 19 and 20, 1962.

Tri-State Radiological Society
Secretary, Dr. John Marchand, 118 S.E. First St., Evansville, Ind. Meets third Wednesday of Oct., Jan., March and May, 8:00 P.M. at Elks Club in Evansville.

University of Michigan Department of Roentgenology Staff Meeting
Meets each Monday evening from September to June, at 7:00 P.M. at University Hospital.

Upper Peninsula Radiological Society
Secretary, Dr. A. Gonty, Menominee, Mich. Meets quarterly.

Utah State Radiological Society
Secretary, Dr. Richard Y. Card, St. Mark's Hospital, Salt Lake City, Utah. Meets fourth Wednesday in January, March, May, September and November at Holy Cross Hospital.

Virginia Radiological Society
Secretary, Dr. Powell G. Dillard, Jr., 715 Church Street, Lynchburg, Va. Meets annually in October.

Washington State Radiological Society
Secretary, Dr. Joseph T. Houk, 14303 Ambaum Blvd., Seattle 66, Wash. Meets third Monday of each month from September through April at the University of Washington Medical School.

West Virginia Radiological Society
Secretary, Dr. Karl J. Myers, 112 N. Woods St., Philippi, W. Va. Meets concurrently with Annual Meeting of West Virginia State Medical Society; other meetings arranged by program committee.

Westchester Radiological Society
Secretary, Dr. Anthony A. Maglione, Westchester Academy of Medicine, Section on Radiology, Purchase, N. Y. Meets on third Tuesday of January and October and on two other dates.

Wisconsin Radiological Society
Secretary, Dr. Howard G. Bayley, 116 Iroquois Parkway, Beaver Dam, Wis. Annual meeting each spring in various places.

Cuba, Mexico, Puerto Rico and Central America

Asociación de Radiólogos de Centro America y Panamá. Comprising: Guatemala, El Salvador, Honduras, Nicaragua, Costa Rica and Panamá.
Secretary-General, Dr. Julio Toriello, 11 Calle 2-37, zona 1, Guatemala. Meets annually in a rotating manner in the six countries.

Sociedad de Radiología de El Salvador
Secretary, Dr. Rafael Vega Gómez.

Sociedad de Radiología de Guatemala
Secretary, Dr. Carlos E. Escobar, 9ª. Calle A 0-05, Zona 1, Guatemala.

Sociedad de Radiología y Fisioterapía Cubana
Secretary, Dr. Miguel A. García Plasencia, Hospital Curie, 29 y F, Vedado, Habana, Cuba. Meets monthly at Curie Hospital.

Sociedad Costarricense de Radiologia
Secretary, Dr. James Fernández Carballo, Apartado VIII, San José, Costa Rica.

Sociedad Mexicana de Radiología, A. C.
Calle del Oro No. 15. México 7, D. F
Secretary-General, Dr. E. Alvarez Hernández. Meets first Monday of each month.

Asociación Puertorriqueña de Radiología
Secretary, Dr. R. B. Díaz Bonnet, Suite 504, Professional Bldg., Santurce, Puerto Rico.

Sociedad Radiológica Panameña
Secretary, Dr. L. Arrieta Sánchez, Apartado No. 6323, Panamá, R. de P. Meets monthly in a department of radiology of a local hospital, chosen at preceding meeting.

Sociedad Radiológica de Puerto Rico
Secretary, Dr. César E. Rosa-Perez, Fondo del Segura del Estado, Parada 1, San Juan 8, Puerto Rico. Meets second Thursday of each month at 8:00 P.M. at the Puerto Rico Medical Association Bldg. in San Juan.

British Commonwealth of Nations

Association of Radiologists of the Province of Quebec
Secretary, Dr. Odilon Raymond, 5400 Blvd. Gouin. Quest, Montreal, Que. Meets four times a year.

British Institute of Radiology
Honorary Secretary, Dr. R. D. Hoare, 32 Welbeck St., London, W. 1. Meets monthly from October until May.

Edmonton and District Radiological Society
Secretary, Dr. S. C. Windle, 105 Northgate Bldg., Edmonton, Alberta. Meets first Tuesday of each month, Oct. to May.

Faculty of Radiologists
Honorary Secretary, Dr. R. A. Kemp Harper, 47 Lincoln's Inn Fields, London, W.C.2, England. Annual meeting to be announced.

Section of Radiology of the Royal Society of Medicine (Confined to Medical Members)
Meets third Friday each month at 4:45 P.M. at the Royal Society of Medicine, 1 Wimpole St., London, W. 1.

Canadian Association of Radiologists
Honorary Secretary, Dr. Robert G. Fraser, *Associate Honorary Secretary*, Dr. Jean-Louis Léger, 1555 Summerhill Ave., Montreal 25, Que. Annual meeting: Marlborough Hotel, Winnipeg, Man., Jan. 22–24, 1962.

Montreal Radiological Study Club
Secretary, Dr. F. McConnell, 1650 Cedar Ave., Montreal, Quebec. Meets first Tuesday evening, October to April.

Section of Radiology, Canadian Medical Association
Secretary, Dr. C. M. Jones, Inglis St., Ext. Halifax, N. S.

Société Canadienne-Française d'Electro-Radiologie Médicale
General Secretary, Dr. Maurice Dufresne, 1560 Sherbrooke (East), Montreal, Canada. Meets third Saturday each month.

Toronto Radiological Society
Secretary, Dr. Wallace M. Roy, St. Joseph's Hospital, 30 The Queensway, Toronto 3, Ontario. Meets second Monday of each month September through May.

College of Radiologists of Australia
Honorary Secretary, Dr. E. A. Booth, c/o British Medical Agency, 135 Macquarie St., Sydney, N.S.W., Australia.

South America

Asociación Argentina de Radiología
Secretary, Dr. Lidio G. Mosca, Avda. Gral. Paz 151, Córdoba, Argentina. Meetings held monthly.

Ateneo de Radiologia
Secretary, Dr. Victor A. Añaños, Instituto de Radiologia, Santa Fe 3100, Rosario, Argentina. Meets monthly on second and fourth Fridays at 7:00 P.M. in the Hospital Nacional del Centenario, Santa Fe 1300, Rosario.

Colégio Brasileiro de Radiologia
Secretary-General, D. Camillo Segreto, Avenida Angélica, 1.170, Caixa Postal 5984, São, Paulo, Brazil.

Sociedad Argentina de Radiología, Junta Central, Buenos Aires
Secretary, Dr. Edgardo O. Olcese, Santa Fé 1171, Buenos Aires. Meetings are held monthly.

Sociedad Bolivana de Radiología
Secretary, Dr. Javier Prada Méndez, Casilla 1596, La Paz, Bolivia. Meets monthly. General assembly once every two years.

Sociedade Brasileira de Radiologia
Secretary, Dr. Nicola Caminha, Av. Mem. de Sa, Rio de Janeiro, Brazil. General Assembly meets every two years in December.

Sociedade Brasileira de Radioterapia
Secretary, Dr. Oscar Rocha von Pfuhl, Av. Brigadeiro Luiz Antonio, 644 São Paulo, Brazil. Meets monthly on second Wednesday at 9:00 P.M. in São Paulo at Av. Brigadeiro Luiz Antonio, 644.

Sociedad Chilena de Radiología
Secretary, Dr. J. P. Velasco, Avenida Santa María 0410, Santiago, Chile. Meets fourth Friday of each month.

Sociedad Colombiana de Radiologia
Secretary, Dr. Alberto Mejía Diazgranados, Carrera 13, No. 25–31, Apartado aéreo No. 5804, Bogotá, Colombia. Meets last Thursday of each month.

Sociedad Ecuatoriana de Radiología y Fisioterapía
Secretary, Dr. Publio Vargas P., Casilla 1242, Guayaquil, Ecuador.

Sociedad Paraguaya de Radiología
Secretary, Dr. Miguel González Addone, 15 de Agosto 322, Asunción, Paraguay.

Sociedad Peruana de Radiologia
Secretary, Dr. Luis Pinillos Ganoza, Apartado 2306, Lima, Perú. Meets monthly except during January, February and March, at Asociación Médica Peruana "Daniel A. Carrión," Villalta 218, Lima.

Sociedad de Radiologia del Atlantico
Secretary, Dr. Raul Fernandez, Calle 40 #41-110, Baranquilla, Colombia. Society meets monthly at the Instituto de Radiologia.

Sociedad de Radiología, Cancerología y Física Médica del Uruguay
Secretary-General, Dr. Ernesto H. Cibils, Av. Agraciada 1464, piso 13, Montevideo, Uruguay.

Sociedade de Radiologia de Pernambuco
Secretary, Dr. Manoel Medeiros, Instituto de Radiologia da Faculdade de Medicina da Universidade do Recife, Caixa Postal 505, Pernambuco, Brazil.

Sociedad de Roentgenologia y Medicina Nuclear de la Provincia de Córdoba
Secretary-General, Dr. Carlos A. Oulton, Santa Rosa 447, Córdoba, Argentina.

Sociedad Venezolana de Radiología
Secretary-General, Dr. Rubén Merenfeld, Apartado No. 9362, Candelaria, Caracas, Venezuela. Meets monthly third Friday at Colegio Médico del Distrito Federal, Caracas.

Continental Europe

Österreichische Röntgen-Gesellschaft
President, Dr. Konrad Weiss, Mariannengasse 10, Vienna 9, Austria. Meets second Tuesday of each month in Allgemeine Poliklinik.

Société Belge de Radiologie
General Secretary, Dr. S. Masy, 256 Chaussée de Wavre, Heverlee-lez-Louvain, Belgium. Meets in February, March, May, June, October, November and December.

Société Française d'Electroradiologie Médicale, and its branches: Société du Sud-Ouest, du Littoral Méditerranéen, du Centre et du Lyonnais, du Nord, de l'Ouest, de l'Est, et d'Alger et d'Afrique du Nord. Central Society meets third Monday of each month, except during July, August and September, rue de Seine 12, Paris.
Secretary-General, Dr. Ch. Proux, 9, rue Daru, Paris 8e, France.

Československá Společnost pro Roentgenologii a Radiologii
Secretary, Dr. Robert Poch, Praha 12, Šrobárova 50, Czechoslovakia. Meets monthly except during July, August, and September. Annual general meeting.

Deutsche Röntgengesellschaft
Secretary, Professor Dr. med. H. Lossen, Universitäts-Röntgeninstitut. Lagenbeckstr. 1, Mainz, Germany. Annual meeting to be announced.

Società Italiana di Radiologia Medica e di Medicina Nucleare
Secretary, Dr. Ettore Conte, Ospedale Mauriziano, Torino, Italy. Meets annually.

Nederlandse Vereniging voor Electrologie en Röntgenologie
Secretary, Dr. J. R. von Ronnen, Violenweg 14, den Haag, Netherlands.

Scandinavian Roentgen Societies
The Scandinavian roentgen societies have formed a joint association called the Northern Association for Medical Radiology, meeting every second year in the different countries belonging to the Association.

Sociedad Española de Radiología y Electrología Médicas y Medicina Nuclear
Secretary, Dr. D. Aureo Gutierrez Churruca, Esparteros, No. 9, Madrid, Spain. Meets monthly in Madrid.

Schweizerische Gesellschaft für Radiologie und Nuklearmedizin (Société Suisse de Radiologie et de Médecine Nucléaire)
Secretary, Dr. Max Hopf, Effingerstrasse 47, Bern, Switzerland.

India

Indian Radiological Association
Secretary, Dr. R. F. Sethna, Navsari Building, Hornby Road, Bombay 1, India.

VOL. 86, NO. 4

ABSTRACTS OF RADIOLOGICAL LITERATURE

Department Editor: T. LEUCUTIA, M.D., Harper Hospital, Detroit 1, Michigan

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ROENTGEN DIAGNOSIS

Head

Cecchini, A., and De Donato, E. I meningiomi delle docce olfattorie. (Meningiomas of the olfactory grooves.) *Radiol. med.*, Dec., 1960, *46*, 1150–1158. (From: Reparto Radiologico, Istituto Neurologico "Carlo Besta" di Milano, Italy.)

The authors present an analysis of the roentgenologic findings in meningiomas of the olfactory grooves, as noted on routine roentgenograms of the skull, or on roentgen studies of the central nervous system with contrast media. Nine cases were males and 17 females; the average age at the time of admission was forty-six years. Surgical intervention showed that in 7 cases the meningioma involved only one olfactory groove, while in 10 cases the involvement was bilateral, and in 9 cases, although the meningioma involved both olfactory grooves, there was a greater involvement on one side.

The roentgen findings noted on plain skull roentgenograms are several: (1) calcifications were present in 5 cases (19.2 per cent), and all appeared above the ethmoidal-sphenoidal plane; (2) localized condensation of bone was present in 15 cases (57.6 per cent)—from a simple osteosclerosis (7 cases, 26.9 per cent), to a thickening of the floor of the anterior fossa (6 cases, 23 per cent), or to a localized hyperostosis (2 cases, 7.7 per cent). These changes were in 11 cases limited to the midline and were symmetric, in the remaining 4 cases they involved only one side; (3) localized osteolytic lesions were noted only in 2 cases, in both at the point of origin of the meningioma; and (4) bony lesions secondary to increased intracranial pressure were present in 18 cases (69.2 per cent).

The roentgen findings in cerebral angiography are such as to permit a correct diagnosis of the site and nature of a meningioma of the olfactory groove. The most common sign is a posterior displacement of the anterior cerebral artery and its frontal branches, as it appears on the lateral angiograms. The angiographic findings in the anteroposterior view depend on the site and extent of the meningioma. In the venous stage there is a posterior displacement of the central veins. In only 8 cases (30.7 per cent) was there pooling of the contrast medium in correspondence with the site of the meningioma. In 12 cases (46.1 per cent) there was involvement of the ophthalmic artery and its branches.

Pneumoencephalography was performed in only 10 cases and generally at the beginning of the clinical investigation and before cerebral angiography. The characteristic findings are an indentation produced by the neoplasm on the frontal horn or horns and on the anterior part of the third ventricle; these were present in 8 cases. The cisterns in the region of the sella turcica were involved in 7 cases; in a few patients there was a block at the level of the cisterna chiasmatis and of the lamina terminalis, which, however, were always displaced posteriorly. In 1 case there was a complete cisterno-ventricular block.

In the opinion of the authors, the roentgen findings observed on plain skull roentgenograms and on cerebral angiograms are in almost all cases sufficient to make the correct diagnosis. In certain cases, in the so-called olfactory-tubercular meningiomas, the neoplasm cannot easily be differentiated from a meningioma arising from the tuberculum sellae. The glioma of the chiasm, the craniopharyngioma, the chordoma of the clivus, etc. have characteristics which differentiate them from the meningioma of the olfactory grooves.—*A. F. Govoni, M.D.*

Keirns, M. M. The angiographic demonstration of cerebral occlusive disease. *South. M. J.*, May, 1961, *54*, 470–475. (From: The Department of Radiology, Baptist Memorial Hospital, Memphis, Tenn.)

The author and his associates have performed 3,000 angiographic studies of the intracranial and neck vessels. Of these cases, only 0.8 per cent died or had permanent hemiplegia within twenty-four hours after the angiographic procedure; several of them had pre-existing disease sufficient to cause death. An additional 2 per cent had mild reactions with complete recovery.

The six methods used were: (1) direct percutaneous injection of the common carotid and the vertebral arteries; (2) retrograde carotid injection accomplished by compressing the carotid artery distal to the needle, thereby demonstrating its origin; (3) vertebral injection; (4) direct subclavian injection; (5) retrograde catheterization of the innominate artery through the right carotid; and (6) brachial artery catheterization. The brachial and direct subclavian injections are not considered to be satisfactory methods. Pneumothorax and mediastinal hemorrhage occurred too often with subclavian punctures. Over 40 per cent of the patients experienced mediastinal hemorrhage.

Three types of occlusive disease occur in the neck and head vessels: (1) localized plaque formation, (2) multiple widespread plaque formation, and (3) generalized constriction of many cerebral vessels. The association of some of these lesions with various types of strokes is discussed.—*Frank M. Windrow, M.D.*

Crawford, E. Stanley, DeBakey, Michael E., Morris, George C., Jr., and Fields, William S. Treatment of stroke by arterial reconstructive operation. *South. M. J.*, May, 1961, *54*, 476–485. (From: The Cora and Webb Mading Department of Surgery and the Department of Neurology, Baylor

University College of Medicine, Houston, Tex.)

Angiographic studies were done on 895 patients in whom extracranial lesions were suspected. Lesions were demonstrated in 336 of these cases. Bilateral carotid and bilateral trans-subclavian vertebral angiography was done on 861 consecutive patients. Thoracic angioaortography was performed when occlusion at the origin of the vessels from the aorta was suspected. The common sites of occlusion were at the bifurcation of the common carotid, at the origin of the common carotid, or at the origin of the vertebral, innominate or subclavian arteries.

Seventeen patients were treated because of troublesome ear noises or systolic murmurs in the neck. There were 292 patients with neurologic disturbances. The neurologic findings are quite variable due to multiple occlusive changes and also to the variable collateral circulation. The classic symptoms produced by occlusion of the various vessels are outlined by the authors. Systolic murmurs are frequently heard at the site of partial occlusions. Diminished pulsation of the vessels and diminished blood pressure distal to involved vessels are important physical findings. The authors suggest routine angiographic studies of all patients who have suffered a stroke.

Of the 458 lesions treated surgically, 12 involved the external carotid, 309 the internal carotid, 20 the common carotid, 23 the innominate, 41 the subclavian and 53 the vertebral arteries. Operability depended on the location and extent of the occlusion and the status of the peripheral vessels. Patients with transient ischemic attack, strokes which have cleared and strokes with progressive improvement have a good prognosis. Others usually have multiple lesions and respond less satisfactorily to reconstructive vascular surgery.

The two procedures usually employed were endarterectomy and end-to-side bypass graft. The techniques of each procedure, the anesthesia and the postoperative care are discussed.

The surgical results are tabulated and discussed. They show a remarkable improvement in the prognosis for patients afflicted with strokes.—*Frank M. Windrow, M.D.*

Keirns, M. M. Radiologic diagnosis of intracranial aneurysms and vascular malformations. *South. M. J.*, May, 1961, *54*, 485–492. (From: The Department of Radiology, Baptist Memorial Hospital, Memphis, Tenn.)

In the past twelve years 3,000 cerebral arteriographies were done; 140 aneurysms and 22 arteriovenous malformations were diagnosed.

Aneurysms are visualized as small pools of contrast material lying outside the usual contour of the normal vessel, most commonly in the vicinity of a bifurcation and frequently in the circle of Willis. Bleeding is evidenced by displacement of vessels or a small "teat-like" protrusion of the opaque medium from the aneurysm. Spasm of a vessel is indirect evidence of bleeding. Because of the frequency of multiple lesions it is necessary to determine the exact point of origin of the bleeding if possible. Oblique roentgenograms sometimes help to demonstrate the neck of the aneurysm. "Berry aneurysms" found about the circle of Willis are due to congenital malformations and are found in young people. Arteriosclerotic aneurysms are usually along the course of a vessel in patients over thirty years of age.

It is desirable to determine whether cross-filling of the aneurysm occurs from the opposite side in order to properly treat the case. Both the carotid and vertebral arteries should be demonstrated because of the frequency of multiple aneurysms.

Arteriovenous malformations show large dilated feeding arteries, serpiginous vessels in the lesion, and very rapid transit of contrast material through the lesion.

The definitive diagnosis of intracranial aneurysms or arteriovenous malformations is almost wholly dependent on cerebral arteriography.—*Frank M. Windrow, M.D.*

Neck and Chest

Arcilla, Rene A., and Gasul, Benjamin M. Congenital aplasia or marked hypoplasia of the myocardium of the right ventricle (Uhl's anomaly); clinical, angiocardiographic, and hemodynamic findings. *J. Pediat.*, Mar., 1961, *58*, 381–388. (From: The Pediatric Cardiophysiology Department, Cook County Children's Hospital and Hektoen Institute for Medical Research, and the Department of Pediatrics, University of Illinois College of Medicine, Chicago, Ill.)

The authors report the angiocardiographic and hemodynamic findings in a proved case of congenital aplasia or marked hypoplasia of the myocardium of the right ventricle.

The clinical findings consisted of progressive heart failure in infancy, marked cardiomegaly, feeble triple heart tones, no significant murmur, and absence of clinical evidence of right ventricular hypertrophy, pulmonary hypertension, or tricuspid regurgitation. The chest roentgenograms demonstrated marked cardiac enlargement with normal or diminished pulmonary vascular markings. The electrocardiogram showed right atrial hypertrophy and left ventricular hypertrophy. Cardiac catheterization revealed normal systolic pressures and markedly elevated presystolic waves in the right ventricular and pulmonary arterial pressure curves which were identical with the right atrial "a" waves.

The angiocardiograms demonstrated enlarged right heart chambers, diminished pulmonary blood

flow, unusual thinness of the right ventricular wall, and conspicuous absence of its trabeculae.

The authors suggest a superior vena cava-right pulmonary artery anastomosis for palliative treatment of this anomaly.—*James F. Martin, M.D.*

Löhr, H., Loogen, F., and Vieten, H. Die periphere Pulmonalstenose. (Peripheral pulmonary stenosis.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, Mar., 1961, *94*, 285–304. (Address: Prof. Dr. H. Vieten, Moorenstr. 5, Düsseldorf, Germany.)

Peripheral pulmonary stenosis, as defined by the authors of this article, refers to any stenotic area distal to the pulmonary valve in the course of the pulmonary arterial circulation. It includes single or multiple lesions. The recorded incidence of this condition is relatively small, chiefly because of the paucity of symptoms and because associated cardiovascular anomalies frequently dominate the clinical picture and diagnostic methods.

Three main types are recognized: Form I includes single or multiple stenoses of the pulmonary artery of lobar, segmental, or lesser caliber; Form II refers to stenoses of one or both main pulmonary arteries at varying distances from the main stem and usually associated with marked post-stenotic dilatation of the involved vessel; Form III comprises stenoses of the supravalvular portion of the main stem that are not accompanied by any appreciable post-stenotic dilatation.

Of 2,500 patients with congenital vascular anomalies, peripheral pulmonary stenosis was found in 0.44 per cent. In this study, only those cases with isolated peripheral pulmonary stenosis were considered with regard to the hemodynamics, clinical picture, prognosis and differential diagnosis.

The hemodynamics in stenosis of a single peripheral artery is essentially normal, whereas in Form III it is similar to pulmonary valvular stenosis. The findings in Form II are not remarkable under normal conditions with the patient at rest. Occasionally, in Form II there may be a pressure difference in the systolic phase between pre- and post-stenotic levels, but the measurements are equal during diastole.

The most reliable diagnostic method is selective intravascular catheterization. With this procedure, if there is a diastolic as well as a systolic differential in a main pulmonary branch, one should suspect stenosis of the contralateral main branch or multiple stenoses in the contralateral lung. If both main stems are stenotic, it is rare to find any marked prestenotic hypertension. This is also true for supravalvular stenosis.

The clinical picture depends on the height of the pressure. If the pressure is low, symptoms are usually absent. Patients with high grade hypertension have exertional dyspnea, marked cyanosis and easy fatigability. Intravascular phonocardiography is particularly valuable in ascertaining the type of murmur. A pure systolic murmur is a frequent finding. A continuous systolic and diastolic murmur is typical and is always registered in the post-stenotic portion. The roentgen findings include a prominent pulmonary artery segment and wide central and fine peripheral vessels in the lungs, with or without dilatation of the right side of the heart.

While supravalvular stenosis is quite similar to pulmonary valvular stenosis, the latter is not associated with a prominent pulmonary artery segment but does produce a loud P2 sound, which is of diagnostic help. Because of the type of murmur, peripheral pulmonary stenosis must be distinguished from patent ductus, particularly if the murmur is maximal in the second left intercostal space in the parasternal line. Patent ductus is associated with increased pulmonary vascularity. Such entities as arteriovenous fistula, aortopulmonary septal defect and pulmonary thrombosis are most easily differentiated by means of angiocardiography and selective catheterization.—*J. Zausner, M.D.*

Johnson, Philip M., Wood, Ernest H., Pasternack, Bernard S., and Jones, Morris A. Roentgen evaluation of pulmonary arterial pressure in mitral stenosis. *Radiology*, Apr., 1961, *76*, 541–547. (Address: P. M. Johnson, 141 Central Avenue, Montclair, N. J.)

The purpose of this paper is to review attempts made in the past to relate roentgen findings to pulmonary arterial pressure and to report the value of newly devised multiparameter formulas for the purpose.

Roentgenograms of the chest give reliable quantitative evidence of pulmonary hypertension in mitral stenosis. As pointed out by Kerley, the peripheral basal linear markings, which he called B-lines, may be produced by pulmonary venous hypertension. The development of B-lines in mitral stenosis is presumptive evidence of pulmonary venous hypertension. Their occasional presence during left ventricular failure and chronic passive congestion has been noted. B-lines are usually seen in cases with pulmonary "capillary" pressures above 20 to 30 mm. Hg and are invariably present when the mean left atrial pressure is in excess of 24 mm. Various investigators have measured the width of the upper portion of the descending branch of the right pulmonary artery to determine the relationship between pulmonary arterial pressure and vessel width. It was concluded that the upper limit of normal width was 14 mm. Significant pulmonary hypertension was found in all patients with a vessel width of 15 mm. or more.

Forty-eight patients with pure or predominant mitral stenosis, as established by clinical, laboratory, and cardiac catheterization findings, were investi-

gated by the authors. Measurements of resting mean pulmonary arterial and pulmonary "capillary" pressures were made on all patients. In each patient an erect 2 m. posteroanterior chest roentgenogram, made within a few days after cardiac catheterization, was available for study. From this the following data were obtained: the presence or absence of B-lines; the altitude in millimeters of the pulmonary artery segment; the width in millimeters of the right descending pulmonary artery branch; the "pulmonary arterial size" in centimeters; and the internal thoracic diameter. Regression equations were derived which gave a strong correlation between mean resting pulmonary arterial pressure and four roentgen parameters: the presence or absence of Kerley's B-lines, the height in millimeters of the pulmonary artery segment, the width in millimeters of the right descending pulmonary artery segment branch, and the "pulmonary arterial size" in centimeters.—*A. W. Sommer, M.D.*

McCue, Carolyn M., and Young, R. B. Cardiac failure in infancy. *J. Pediat.*, Mar., 1961, *58*, 330–341. (From: The Department of Pediatrics, Medical College of Virginia, Richmond, Va.)

The authors present a review of 115 consecutive cases of cardiac failure in infancy to emphasize the serious prognosis of congestive heart failure and to stress the importance of early definitive diagnosis.

The primary causes of congestive cardiac failure in 71 per cent of the cases studied were endomyocardial disease, interventricular septal defect, coarctation of the aorta, transposition of the great vessels, patent ductus arteriosus, and aortic atresia. The term "cardiac failure" was used to indicate that the heart had failed to maintain adequate output to supply the metabolic needs of the body. Dyspnea was always present and a cardiac enlargement was noted in all but a few cases.

The following therapeutic principles and/or measures constituted the initial management: (1) oxygen, (2) rest, (3) antibiotics, (4) low salt diets, (5) diuretics, and (6) digitalis.

Although the prognosis for infants with cardiac failure is grave, it seems clear that a progressively larger percentage of them can be salvaged by identification of the underlying lesion and by adequate treatment. This is notably true in respect to patent ductus arteriosus, coarctation of the aorta, paroxysmal supraventricular tachycardia, pulmonic stenosis, myocarditis, and severe anemia.—*James F. Martin, M.D.*

Thurn, P., Schaede, A., Hilger, H. H., and Düx, A. Der Ventrikelseptumdefekt im selektiven Laevokardiogramm. (Ventricular septal defect in selective levocardiography.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, Mar., 1961, *94*, 305–323. (Address: Prof. Dr. P. Thurn, Med. Klinik der Univ., Bonn-Venusberg, Germany.)

Selective levocardiography is the best method for accurate localization of ventricular septal defects with left to right shunt, whether isolated or multiple defects exist. It is particularly valuable when the defect is small, since this method can distinguish membranous from muscular defects. It is likewise definitive for the differential diagnosis of isolated intra-atrial septal defect and one combined with a ventricular septal defect. Also, a common atrioventricular channel can be differentiated from a combined intra-atrial and ventricular septal defect, particularly with the direct opacification of the right atrium from the left ventricle. In addition, levocardiography is successful in demonstrating aortic valvular insufficiency with subvalvular septal defect and differentiating this combination from ductus arteriosus or aortopulmonary defects.

Selective levocardiography affords the advantage of an unobstructed view of the outflow tract of the right and left ventricles. There are no overlying pulmonary vessels. Opacification is maximal because there is no dilution of the contrast material in the lungs or the left atrium. A rapid filming technique is essential. The best topographic results are obtained by simultaneous exposures in lateral and left anterior views. These projections also furnish information concerning the size of the defect, the caliber of the aorta and the ratio of the aortic to pulmonary diameter. In general, the size of the defect is less important than its proportional relationship to the diameter of the aorta.

In membranous defects, the contrast material flows from the left into the right ventricle chiefly in a caudal direction on the posterior wall, leaving the anterior wall (outflow tract) relatively unaffected. The shunted blood flows during systole in a dorsocaudal direction, whereas the diastolic flow occurs in the ventrally situated outflow tract. It has been determined that, in membranous defects, the shunt occurs during ventricular systole, while the shunt takes place during ventricular diastole if the defect is muscular and especially when it is small. Incidentally, a small muscular defect is of no real significance, since it usually closes during systole.

A dilated left ventricle associated with a relatively small aorta and wide pulmonary artery indicates a large left to right shunt, which will produce better contrast filling of the pulmonary arteries than a small left to right shunt. A slightly dilated left ventricle, with an aorta and pulmonary artery of equal caliber, indicates a weak shunt. A very marked dilatation of the left ventricle is usually combined with a ventricular and atrial septal defect.

A common atrioventricular chamber with an atrial septal defect produces a left to right shunt. The common chamber with a ventricular septal defect

will do likewise as long as the resistance in the lesser circulation is lower than in the general circulation. In this anomaly, during systole, the shunt is usually from the left ventricle to the right atrium, but, occasionally, it is from the right ventricle to the left atrium or from the left atrium to the right ventricle. An associated anomaly of the mitral valve may cause a shunt from the left ventricle to the left atrium. Similarly, an anomaly of the tricuspid valve may cause a reflux from the right ventricle to the right atrium. If an associated ventricular septal defect is not appreciable, the shunt is from the left ventricle to the right atrium. With a large ventricular septal defect, two shunts may be seen: from the left ventricle to the right atrium and simultaneous filling of the pulmonary artery and right atrium. This occurs particularly if there is a high septal defect.—*J. Zausner, M.D.*

Lehman, J. Stauffer. An evaluation of cardiovascular contrast media. *Radiology*, Apr., 1961, *76*, 548–563. (Address: 230 N. Broad Street, Philadelphia 2, Pa.)

The increased use of cardiovascular opacifying procedures for the diagnosis of congenital malformations of the heart and great vessels and for the study of acquired cardiovascular disease has led to a search for and development of many new radiopaque media. None of the methods of evaluating these conditions is completely devoid of danger to the patient and most of the hazards are due to the injected radiopaque medium. Because of this, the author has investigated the physicochemical and toxicologic properties of the various contrast media he has used in his clinical studies of the heart, intrathoracic vessels and pulmonary circulation. Since a good contrast agent should possess, in addition to an absence or low degree of toxicity, good radiodensity and low viscosity, and hence easy injectability, additional studies were made from the standpoint of viscosity, flow rates through catheters, phantom radiodensity and comparative angiocardiographic opacification in experimental animals. Reactions were also tabulated in a series of clinical studies made with certain of the media.

The viscosity studies were conducted at three different temperatures. They revealed that hypaque sodium 50 per cent had the lowest and cardiografin 90 per cent the highest viscosity. The viscosity of each of the media tested decreased as the temperature was raised. Flow rates through catheters were influenced most by the size of the catheter. Large bore catheters, at the high injection pressure applied, permitted a high rate of flow of each of the tested solutions, closely approximating that of water. As the catheter bore was decreased, differences in the rate of flow became more evident. Cardiografin 90 per cent was found to have the slowest rate of flow, while hypaque-M 50 per cent and miokon sodium 50 per cent were found to have the most rapid rates.

Animal toxicity studies showed that the cerebrotoxic and cardiotoxic effects are somewhat dependent upon the chemical nature and concentration of the contrast agent, more dependent upon the amount injected, and to a certain extent upon the site of injection. These studies were limited to toxicity comparisons of two of the newer preparations, ditriokon and renovist, with two of the older media, diodrast 70 per cent and urokon 70 per cent. Ditriokon and renovist were found to be less toxic to the animals (dogs) tested than diodrast 70 per cent.

Radiodensity studies were done with the use of a plastic block phantom as well as a testing procedure employing dogs under conditions simulating clinical cardiovascular opacification studies. While electronic densitometer recordings showed lower, medium and higher range radiopacity readings in the phantom procedure, the test procedure on dogs showed little over-all difference in the degree of opacification produced by the several media as determined visually.

Clinical studies for the most part with ditriokon, renovist, and hypaque 75 per cent have given the general impression that the incidence of reactions is about the same for all and that the degree of such reactions is very similar. The author believes that the reactions are definitely less marked as compared with his previous experiences using the more concentrated media such as diodrast 70 per cent and urokon 70 per cent. A considerably wider margin of safety is also felt to be present with the less concentrated media.

It is the opinion of the author that factors such as catheter type, size and length, pressure injection, injection rate, catheter positioning, rapid serial roentgenography or cineroentgenography, the amount of injected medium, and the technique of injection using the most favorable catheter location for the most informative study are of more importance and significance than minor differences in absolute radiodensity and small variations in iodine content of the several cardiovascular radiopaque agents. He concludes with the statement that renovist, of moderate iodine content, effective radiodensity, comparatively low viscosity, and a good flow rate through catheters appears to be one of the most satisfactory cardiovascular contrast preparations he has employed.—*Donald N. Dysart, M.D.*

Doyle, F. H., Read, A. E., and Evans, K. T. The mediastinum in portal hypertension. *Clin. Radiol.*, Apr., 1961, *12*, 114–129. (From: The Departments of Radiodiagnosis and Medicine, Hammersmith Hospital, London W.21, and Postgraduate Medical School of London, England.)

In portal hypertension due to intrahepatic or extrahepatic obstruction, some of the blood returning from the splanchnic bed bypasses the liver and is

shunted by collateral channels to the systemic venous system. These collateral channels ultimately drain into the superior and inferior venae cavae. The terminal part of the azygos vein, which joins the superior vena cava a short distance above the pericardium, is the "final common path" of all these routes. Any prolonged and considerable increase in the volume of blood flowing through the azygos and hemiazygos veins might be expected to result in an increase in their diameters.

The azygos vein in the thorax runs in a cephalad direction anterior to the vertebral bodies as far as the fourth or fifth dorsal vertebra. It is joined in front of the vertebral column by the superior and inferior hemiazygos veins. At the level of the fourth or fifth thoracic vertebral body, the azygos vein arches forward over the root of the right lung, passes close to the trachea in the right tracheobronchial angle, and joins the superior vena cava on its posterior aspect.

The method used in this study for the roentgen demonstration of the azygos vein was that of anteroposterior laminagraphy. The segment of the azygos vein which lies in the right tracheobronchial angle adjacent to the trachea is peculiarly well suited to laminagraphic demonstration. Its lateral margin is covered by mediastinal pleura and is clearly delineated against the aerated lung. The medial margin is not normally discernible, but the inner wall of the trachea is sharply defined against the shadow of air in the trachea. The size of the azygos vein shadow is largest when the patient is supine, smallest when the patient is erect, and intermediate when the patient is sitting. The exposure is made without delay at the end of a normal expiration—the size of the azygos vein being larger in expiration than in inspiration. Three laminagraphic sections are routinely made at intervals of 1 cm. using a multisection cassette. Nearly always the azygos vein is shown best in sections at levels 8, 9 or 10 cm. above the table top.

The criteria of portal hypertension accepted for this investigation were that the patient should have evidence of esophageal or gastric varices on barium swallow and/or collateral channels demonstrated by splenic venography. However, these criteria do not in every instance imply a raised portal pressure. In some cases of portal obstruction, the collateral vessels develop to such an extent that the portal pressure falls to normal levels.

The measured diameters of the azygos veins were plotted against age, sex, height, weight and body surface area and the only significant correlation was found to be with the weight of the patient. This correlation is statistically highly significant. Because of this finding, the diameters of the azygos veins in both control and portal hypertensive groups were corrected to a standard patient weight of 140 pounds. If all other causes of azygos vein enlargement are excluded, a patient with an azygos vein diameter of 20 mm. or more, measured by the method described, is almost certain to have portal hypertension.

The hemiazygos venous system is commonly represented as a superior and an inferior hemiazygos vein, each lying in front of the left side of the thoracic vertebral bodies and each draining into the azygos vein in front of the vertebral column. Explanations for the formation of the left paravertebral shadow seen on an anteroposterior roentgenogram of the thoracic spine vary. Billing and Knutsson imply that it is due to the pleural reflection between the descending aorta and the vertebral column. Gladnikoff, in his monograph on the mediastinum, introduces evidence to suggest that it is due to the hemiazygos vein. At all ages the left paravertebral shadow is, on the average, wider in the patient with portal hypertension than in the control group. Above the age of forty-five years, some factor or factors unrelated to portal hypertension are present which result in widening of the left paravertebral shadow. The factor which seemed to the authors to be the main cause for this was the presence of degenerative disk changes in the thoracic spine. Dilatation and elongation of the descending thoracic aorta is a second factor which may play a part in some cases. In reviewing the roentgenograms of a large series of patients with portal hypertension, a number of cases with very wide left paravertebral shadows were discovered. In all these patients there was clinical evidence of fluid retention, and it seemed plausible to the authors that the explanation of the abnormal width and shape of the left paravertebral shadow in this group lay in the presence of excess fluid in the mediastinum- "mediastinal edema."

The incidence of posterior mediastinal opacities or an abnormal right paravertebral shadow in patients with portal hypertension is not high—approximately 10 per cent. These mediastinal abnormalities occur (invariably, in the authors' experience) in patients who have large esophageal varices demonstrated by barium swallow, and who exhibit numerous large collateral venous channels at splenic venography. The lack of correlation between the size of the azygos vein and the extent of esophageal varices may be an indication that the flow of blood through the esophageal varices is slow, and that they are "poor collaterals," playing little part in reducing portal venous pressure. There is also an absence of correlation between the size of the azygos vein and the presence or absence of ascites, encephalopathy and gastrointestinal bleeding. Some estimate of the size of the azygos vein and of the width of the left paravertebral shadow can often be obtained from a supine anteroposterior roentgenogram of the mediastinum.

While roentgen study of the mediastinum can make an important contribution to the diagnosis of portal hypertension, these mediastinal abnormalities should not be misinterpreted. A dilated azygos vein in the tracheobronchial angle can simulate a tumor. Similarly, a dilated part in the ascending azygos vein

and in other mediastinal veins can simulate tumors. —*Samuel G. Henderson, M.D.*

Abdomen

Hays, Daniel M. Intussusception as a postoperative complication in pediatric surgery. *Surg., Gynec. & Obst.*, May, 1961, *112*, 583–589. (From: The Division of General Surgery, Los Angeles Childrens Hospital, Los Angeles, Calif.)

The author presents 9 cases in which the complication of intussusception occurred during the early postoperative state after laparotomy for other conditions. The cases are reported in great detail.

This complication is observed with sufficient frequency to warrant special consideration when obstruction occurs after laparotomy. The intussuscepta are confined to the small bowel and are rarely associated with rectal bleeding or a palpable abdominal mass. The development of vomiting and distention after the return of gastrointestinal function is characteristic. Roentgenograms usually show mechanical obstruction with intra-abdominal fluid. There is leukocytosis of marked degree.

In children, therapy by intraluminal suction in cases of apparent adynamic ileus or adhesive obstruction should be brief, with recognition of the fact that postoperative intussusception is a real entity and necessitates surgery.—*Eva S. Carey, M.D.*

Rajic, D. S. Some lesions of the colon in infancy and childhood. *Canad. M.A.J.*, Apr. 22, 1961, *84*, 880–886. (From: The Departments of Radiology, War Memorial Children's Hospital, London, Ontario, and the University of Western Ontario, Canada.)

The author discusses Hirschsprung's disease and intussusception of the bowel and emphasizes the contribution of the radiologist in the diagnosis and treatment of these conditions. He describes a new method of fluoroscopy with use of the image intensifier and points out that this is an excellent procedure for studying infants and young children. He feels that it eliminates most of the objections to treatment of intussusception by barium enema.

Hirschsprung's disease is also known as congenital megacolon and, recently, as aganglionic colon. Although the diagnosis is relatively simple it is frequently delayed or missed. The demonstration of a narrow segment of the distal colon and dilatation and hypertrophy of the colon proximal to the narrow segment are usually diagnostic of this condition. It is noted that the rectosigmoid area may be obscured in the plain posteroanterior study and, for this reason, it is felt that oblique roentgenograms of the rectosigmoid area must always be made to avoid missing a small area of aganglionosis. Occasionally a rectal biopsy is indicated in order to make the diagnosis more positive.

Intussusception is described and illustrated by several case reports. Reduction by barium enema is discussed in some detail and the advantages and disadvantages of this method are listed.

The statistics published by Ravitch of the Children's Hospital in Pittsburgh show no significant difference in mortality between the cases treated with barium enema and those treated surgically. The author believes that the reduction in radiation exposure, which can be accomplished by use of the image intensifier, removes the only remaining objection to the reduction of intussusception by barium enema.—*Richard E. Kinzer, M.D.*

Gasster, Marvin, Golden, Ross, Will, Drake, and Mellinkoff, Sherman M. Xanthomatosis involving the colon and small intestine. *Am. J. Digest. Dis.*, Apr., 1961, *6*, 312–321. (From: The Departments of Medicine, Radiology and Pathology, University of California School of Medicine, Los Angeles, Calif.)

This article reports a case of xanthomatosis of the colon in a fifty-four year old female who had been under observation because of induration and swelling of some areas of her skin. Over most of her body the skin was thickened and its color gave it the appearance of a pumpkin. She was intermittently anemic and the blood cholesterol ranged between 300 and 600 mg. per cent. She had chronic disease of the liver.

Mucous membranes of the soft palate and pharynx showed a deposition of yellowish-orange pigmentation. Pigmentation of the rectal mucosa was also noted on proctosigmoidoscopy. She ultimately became jaundiced and died in another hospital, death apparently being due to myocardial infarction, although this was not demonstrated at autopsy.

Barium enema examination of the colon is stated to have revealed variations in the mucosal pattern, but the roentgenograms reproduced in good illustrations are not very convincing. Small bowel changes are also described, but the autopsy record does not mention the small bowel. Microscopic sections from the colon show xanthoma cells in the submucosa only. Unfortunately, the autopsy findings were not correlated with the clinical history.—*Richard E. Kinzer, M.D.*

Crosta, Clemente, and Favero, Pier Alessandro. Sur les résultats obtenus avec l'examen tomographique dans l'étude des voies biliaires au moyen de la cholangiographie intraveineuse. (Results of laminagraphic examination in study of the bile ducts during intravenous cholangiography.) *Radiol. Clin.*, July, 1960, *29*, 224–250. (From:

Institut de Pathologie Chirurgicale de l'Université de Milan, Milan, Italy.)

Laminagraphic examination may be of considerable importance in cholangio-cholecystography. It is very useful for a clear demonstration of the bile ducts and occasionally it is helpful for better visualizing the gallbladder. Laminagraphy aids the examiner in determining more precisely when the biliary system is normal. Also, when pathologic changes are present, the details are more clearly shown.

Laminagrams are usually taken after about twenty minutes if the common bile duct is seen on a routine roentgenogram of the right upper quadrant. If very poor visualization is obtained, an injection of morphine or of other drugs which may cause relative contraction of the spincter of Oddi is given. Laminagrams are usually taken in slightly oblique positions with the first cuts at 7-8-9-10 cm. from the table top.

The results in 71 patients are tabulated and fifteen roentgenographic reproductions. are included.—*Charles M. Nice, Jr., M.D., Ph.D.*

Frimann-Dahl, J. Radiology in tumours of the pancreas. *Clin. Radiol.*, Apr., 1961, *12*, 73–79. (From: The Roentgen Department, Ulleval Hospital, Oslo, Norway.)

Of the intra-abdominal organs, the pancreas is one of the most difficult to examine. Its retroperitoneal position at the height of L_2–L_3 makes palpation of the normal gland nearly impossible and the close connection with the posterior abdominal wall prevents distinction from other organs.

There are mainly two types of tumors which occur in the pancreas—the carcinomas and the cysts. Clinically, carcinoma of the body of the pancreas produces continuous, severe pain, most pronounced when the patient is lying on his back and relieved when he is sitting up. Tumors of the head of the pancreas present with jaundice as the first sign, later associated with pain and vomiting.

In the last decade new methods of investigations have been developed which, to some degree, are superior to the conventional ones. Procedures for the direct or indirect diagnosis of tumors of the pancreas are: (1) conventional gastrointestinal study (including plain roentgenography); (2) pre-, inter- and postoperative cholangiography (using biligrafin); (3) pancreatography during or after operation (establishment of an external fistula and injection of contrast medium); (4) pneumolaminapancreatography (insufflation of retroperitoneal air and inflation of the stomach); (5) aortography (especially by the introduction of a catheter into the celiac artery); and (6) splenoportography.

In the diagnosis of carcinoma of the pancreas, various writers have stressed the demonstration in gastrointestinal studies of indentations or defects in the contour of the stomach or duodenum caused by the tumor and, in addition, changes in the mucosal pattern. Small defects and indentations occur first on the inside of the duodenal loop and in the pyloric region. In these areas they indicate a tumor of the head of the pancreas. The larger indentations on the stomach and colon, related to tumors of the body and tail of the pancreas, may represent either neoplasms, which are usually inoperable, or benign tumors, such as cysts and pseudocysts.

At operative cholangiography, coincident filling of the pancreatic duct for its entire length may occur. Indentation, displacement or deformity of the common duct may indicate the presence of a pancreatic tumor.

A method of pancreatography performed during operation was described by Leger, Gally and Arvay in 1954. Another technique was reported by Macarini and Perassi in 1953. They used a combination of retroperitoneal insufflation, gas in the stomach and transverse axial laminagraphy, making it possible for the first time to see the pancreas directly. If properly done, it is easily performed and safe for the patient. Laminagrams are taken either in the horizontal position, with the patient in lateral recumbency, or in the erect lateral position, and transverse sections are made with the patient sitting or standing upright. In the lateral position, several laminagrams must be taken to include the area from the head to the tail of the pancreas. The gland is then seen to be "floating" in the retroperitoneal air in front of the kidney, bordered anteriorly by the gas-distended stomach. Transverse axial laminagrams are more difficult to obtain and also more difficult to interpret. This is particularly true in thick, heavy individuals. Such studies are often decisive for final diagnosis. In normal cases the retroperitoneal air seems quite regularly to "dissect out" the pancreas, so that the contours are well shown and the gland "floats" in the air. In pathologic cases, when the pancreas is not clearly outlined, the blurred contours may indicate a lesion with some degree of certainty.

Angiography is a valuable aid in studying tumors of the pancreas. Aortography is, in many ways, nearly as effective and may even be better than using selective injection into the celiac artery, because of a simultaneous filling of other vessels. Amundsen has pointed out that downward displacement of the kidney, indicated by a steeper angle of the renal artery, is often noted with tumors of the pancreas. The renal or hepatic artery may be bent caudally, and the aorta is often curved more to the left than normal. When a patient with an aneurysm of the abdominal aorta is admitted with a diagnosis of pancreatic tumor, the aneurysm will probably be overlooked if the examination is limited to injection of the celiac artery, but aortography will reveal the dilated vessel. However, a lateral view is one of the advantages of the selective method, and such a view can hardly be obtained in aortography. Also, by using splenoportography, information can be gained about the pres-

ence of a pancreatic tumor, for instance, by showing invasion of the splenic or hepatic vein.

In summary, the author feels that retroperitoneal insufflation of oxygen combined with laminagraphy is particularly valuable in the diagnosis of tumors of the pancreas.—*Samuel G. Henderson, M.D.*

GYNECOLOGY AND OBSTETRICS

BENNETT, M. F., LYNCH, J., and TWEEDIE, F. J. The erect lateral projection of the pelvis: an assessment of its value as an initial procedure in pelvimetry. *J. Canad. A. Radiologists*, Mar., 1961, *12*, 10–14. (From: The Royal Victoria Hospital, Montreal, Quebec, Canada.)

The authors studied the erect lateral roentgenograms of the pelvis in 317 patients examined in the Royal Victoria Hospital between 1954 and 1958 in an attempt to determine the percentage in whom a vaginal delivery could be predicted. The shortest anteroposterior diameters of the inlet and of the outlet were measured. The shape and inclination of the sacrum, the width of the sacrosciatic notch and the relationship to the presenting part were evaluated. Cephalometry was done when possible.

In a group of 278 cases, uncomplicated vaginal delivery was predicted in 189. This proved to be correct in 181 cases, an accuracy of 95.8 per cent. The error was primarily due to failure to recognize lower pelvic strait disproportion.

The main advantage of this single roentgenogram technique is the reduction in the radiation exposure of the maternal ovaries and of the fetus. The principal deficiencies are related to the impossibility of determining the interspinous diameter and the pelvic shape.—*J. N. Ané, M.D.*

BAGHDASSARIAN, OLGA M., KOEHLER, P. RUBEN, and SCHULTZE, GUNTER. Massive neonatal ascites. *Radiology*, Apr., 1961, *76*, 586–592. (Address: O. M. Baghdassarian, Johns Hopkins Hospital, Baltimore 5, Md.)

The authors review the literature of massive fetal or neonatal ascites and present 3 cases of this rare intraperitoneal accumulation of fluid during prenatal life or shortly after birth. Three large groups of underlying anatomic abnormalities have been implicated in the pathogenesis of this condition: (a) intestinal anomalies such as perforation of the bowel secondary to malformation; (b) portohepatic abnormalities producing obstruction of the portal circulation; and (c) anomalies of the lower urinary tract.

The accumulation of large amounts of fluid in gastrointestinal abnormalities is usually the result of perforation of a viscus secondary to atresia, stenosis, intussusception, volvulus, or herniation. Portohepatic abnormalities produce ascites through intra- and/or extrahepatic obstruction of portal circulation, and are rarely amenable to surgery. Intrahepatic obstruction is the more common and is due to congenital hepatic cirrhosis. Genitourinary abnormalities are associated with atresia of the urethra or urethral obstruction. The method of fluid formation intraperitoneally in urethral obstruction is not clear except in cases of perforation of the bladder, but it may be due to transudation.

Roentgenographically, there is diffuse, homogeneous opacification of the abdomen, with bulging flanks and lack of properitoneal fat lines. When bladder neck obstruction is present, the cystourethrogram is usually diagnostic. The authors stress that neonatal ascites not associated with generalized edema is an emergency situation with a grave prognosis, unless there is prompt correction of the underlying congenital anomaly.—*John S. Alexander, M.D.*

BLOOD AND LYMPH SYSTEM

BOLLER, R., and DEIMER, E. Die perkutane Splenoportographie und der intrasplenale Adrenalintest bei der Leberzirrhose. (Percutaneous splenoportography and the intrasplenic adrenalin test in cirrhosis of the liver.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, Feb., 1961, *94*, 199–207. (From: Medizinische Abteilung des Allgemeinen Krankenhauses in Wien, Vienna, Austria.)

The authors examined 114 patients for hepatic diseases and used as diagnostic criteria the vertical diameter of the spleen on the roentgenogram, intrasplenic pressure values (both before and after intrasplenic injection of adrenalin), evidence of functional and anatomic alterations in the portal venous system, and, finally, the intrasplenic adrenalin test.

The following procedure was employed: A laparoscopic examination is made, which yields valuable macroscopic and microscopic information and permits insertion of a needle into the hilus of the spleen. A pressure gauge is connected to the needle and the intrasplenic pressure is determined. Roentgenograms are made during and after injection of from 40 to 60 ml. of contrast medium. Then, 1/10 mg. of adrenalin is injected into the spleen and the intrasplenic pressures are continuously recorded. At the same time the peripheral blood pressures are determined.

Great splenic enlargement was observed in cases of acute hepatitis and in advanced cirrhosis. In chronic hepatitis and in early cirrhosis, the size of the spleen remained essentially normal.

The intrasplenic pressure was slightly below the portal pressure in normal persons, as well as in patients with fatty degeneration or atrophy of the liver. In inflammatory hepatic diseases and in cirrhosis, the intrasplenic pressures were greatly increased unless there was collateral circulation between the portal and the caval systems.

The observations after intrasplenic injection of adrenalin were as follows: In the normal patient the spleen contracted and the intrasplenic pressure increased by approximately 200 mm. of water. The peripheral blood pressure remained unchanged. Patients with severe cirrhosis, on the other hand, showed increases of only 100 mm., or even negative values. In the presence of portacaval collateral circulation, the increase in intrasplenic pressure was insignificant, but the peripheral blood pressure rose within one minute after the injection of adrenalin.

The authors inject 60 ml. of 76 per cent urografin within six seconds. If the injection of the contrast medium is too forceful and too fast, retrograde filling of the veins occurs, simulating pathologic portacaval collateral circulation. It is of special importance to realize that in those cases the intrasplenic adrenalin test will not result in an elevation of the peripheral blood pressure.—*Wolfgang H. Steinmetz, M.D.*

Vargas, Lester L., and Forsythe, Thomas. A syringe heater for angiocardiography. *Radiology*, Feb., 1961, *76*, 248–250. (Address: Rhode Island Hospital, Providence 2, R. I.)

The authors describe a syringe heater which they designed for use with a mechanical injector. Its purpose is to maintain the radiopaque medium used for angiocardiography at body temperature before and during the injection. This is essential when 90 per cent diatrizoate (hypaque) is used, because this preparation has the disadvantage of separating into crystalline and fluid fractions at room temperature.

The syringe heating device consists of a hollow cylinder, machined from a standard rod of stock aluminum, which fits around a Lehman 50 cc. syringe. A slot along one side permits visualization of the calibrations on the syringe. A copper electrical thermal immersion element supplies the heat by conduction to the aluminum jacket. The solution reaches body temperature in ten to fifteen minutes and the temperature is maintained at that level by a thermostat. The advantages of this heater are its simplicity and its low cost.—*W. M. McBride, M.D.*

Wallace, Sidney, Jackson, Laird, Schaffer, Burton, Gould, John, Greening, Roy R., Weiss, Arthur, and Kramer, Simon. Lymphangiograms: their diagnostic and therapeutic potential. *Radiology*, Feb., 1961, *76*, 179–199. (Address: Department of Radiology, Jefferson Medical College Hospital, Philadelphia 7, Pa.)

A modification of Kinmonth's method of intralymphatic injection was used to demonstrate the lymphatics and lymph nodes of the extremities, including the pelvic, para-aortic, axillary, and supraclavicular areas, as well as the thoracic duct. A mixture containing equal parts of 0.5 per cent Evans blue dye and 1 per cent procaine hydrochloride was injected intradermally into the interdigital web space between the first and second digits to make the lymphatic channels identifiable. Ethiodol was injected slowly into the exposed lymph vessel without undue pressure. Five to 7 ml. of radiopaque material was used for studies of the upper extremity and 10 to 15 ml. in the lower extremity. Roentgenograms were taken at the completion of the injection and again twenty-four hours later. The lymph nodes were best seen on twenty-four hour roentgenograms.

This report presents the results in the lymphangiographic study of 110 patients; 207 extremities were injected (174 lower and 33 upper). The lesions studied were as follows: carcinoma, 54; lymphoma, 28; edema, 12; infection, 5; and miscellaneous, 11. Complications were infrequent and not serious. Two patients experienced transient lymphangitis. Frank wound infection occurred three times.

In lymphedema, the findings varied from an increase to an almost complete absence of channels. Extensive collateral pathways were demonstrated in the presence of obstruction to lymph flow. The normal lymph nodes have a homogeneous reticular pattern. In lymphadenitis, the lymph nodes are larger but normal in architecture; in lymphomas they are enlarged, lacy, and ghost-like; in carcinoma the lymph nodes have a moth-eaten appearance.

Lymphangiography can be used to determine the general type and extent of disease processes; as a guide to lymph node dissection; in radiation therapy for accurate portal placement; and in both radiation therapy and chemotherapy to assess the response to treatment.—*Arno W. Sommer, M.D.*

RADIATION THERAPY

Buttenberg, Dietrich, Schönfelder, Ruth, and Stoll, Peter. Zur Prognose der Strahlentherapie des Kollumkarzinoms nach der "Sensitization Response." ("Sensitization response" in the prognosis of radiation therapy for carcinoma of the cervix.) *Strahlentherapie*, Dec., 1960, *113*, 538–552. (From: Universitäts-Frauenklinik, Heidelberg, Germany.)

In the vaginal smears of 128 patients with carcinoma of the cervix followed during radiation therapy, 44 (34.4 per cent) showed distinct "sensitization response" (Graham), and 84 (65.6 per cent) showed only slight "sensitization response." From two and one-half to five years after therapy, 28 (63.6 per cent) of the patients who had distinct "sensitization response" and 51 (60.7 per cent) of those who had had slight "sensitization response" were free of signs and symptoms of carcinoma of the cervix.

Because of this insignificant difference between

the two groups, the authors have dismissed "sensitization response" as a valid basis for prognosis of the effectiveness of radiation therapy for carcinoma of the cervix.—*Henry G. Moehring, M.D.*

Kolling, Hans-Lothar, and Reuter, Ernst. Strahlenbelastung und Strahlenschutz der menschlichen Linse bei therapeutischen Massnahmen in Augennähe. (Radiation exposure and protection of the human lens in therapy about the eye.) *Strahlentherapie*, Oct., 1960, *113*, 299–311. (From: Institut für Röntgenologie und Strahlenkunde der Universität, Jena, Germany.)

On the basis of measurements in air with various eye shields and in both infant and adult sized phantoms, the authors arrived at the following conclusions in regard to radiation therapy about the eye (their specific concern was treatment of hemangiomas):

(1) To offer protection of consequence, eye shields should fit the bulb and should be made of high lead content glass or, better yet, of approximately 2 mm. of metallic lead.

(2) With radium molds applied anteriorly, even the best lead shields which were tested reduced the irradiation of the lens by only one-third. Eye shields failed to protect the lens from radiation when radium molds were applied about the eye other than anteriorly.

(3) Eye shields can reduce irradiation of the lens by about one-half when interstitial radium is used, particularly when the needles are applied in the lids. Much of this protection results from increasing the distance between the lens and the radium sources.

(4) Treatment of hemangiomas in the region of the eye with contact roentgen therapy and with the eye protected by suitable, effective eye shields exposes the lens to the least radiation hazard.—*Henry G. Moehring, M.D.*

Pohlit, Wolfgang. Die Messung der Neutronenstreustrahlung an einem 35 MeV-Betatron. (Measurement of stray neutrons from a 35 mev. betatron.) *Strahlentherapie*, Nov., 1960, *113*, 469–474. (From: Max-Planck-Institut für Biophysik, Frankfurt/Main, Germany.)

The author diagrams the levels of slow and fast neutron flux around a 35 mev. betatron in a treatment room. He measured slow neutrons with indium foil and fast neutrons with indium foil encased in paraffin cylinders of 12 cm. diameter.

Of the secondary radiations around a betatron operating at more than 20 mev., the bremstrahlung and neutron radiation have approximately equal import (in the range of mrem per hour) for personnel; for the patient, bremstrahlung is more important (1–2 per cent of the primary dose), though neutrons play an equally important role in secondary radiation to the eyes. Radiation activity produced in the ambient air is negligible for both personnel and patient; its maximum is 0.01 per cent of the primary dose.—*Henry G. Moehring, M.D.*

Westfall, Michael P. Radiation nephritis in adults and children; effects of radiation on growing bones. *J. Urol.*, Apr., 1961, *85*, 476–482. (From: The Veterans Administration Hospital, Bronx 68, N. Y.)

In this article, the author bases his findings and recommendations upon a review of 66 adult patients with testicular tumors who were irradiated over the renal area and 15 patients in the younger age group who were irradiated for Wilms' tumor. Of the 66 patients who were irradiated for tumor of the testis, 23 developed urinary tract signs and symptoms suggestive of nephritis; of the 15 patients with Wilms' tumor, 5 developed albuminuria or casts following irradiation of the involved kidney or renal fossa.

Two of the children who were irradiated for Wilms' tumor showed evidence of interference with bone growth—hemivertebral atrophy of the lumbar spine in 1 and arrested growth of the iliac bone in the other.

The author includes a historical survey of other reports of similar radiation damage. His experience is another example of the well-known fact that irradiation will produce damage to normal tissues when given in large amounts and over a long enough period of time. It is unfortunate that the author does not give more specific data regarding the quality and quantity of radiation, and the time factors involved in the production of the changes which he reports.—*George W. Chamberlin, M.D.*

Baudisch, Eberhard. Beitrag zu den Strahlenschäden der Rippen und Schlüsselbeine bei Brustkrebs-Patienten. (Radiation damage to the ribs and clavicles in patients with carcinoma of the breast.) *Strahlentherapie*, Oct., 1960, *113*, 312–318. (From: Institut für Röntgenologie und Strahlenkunde der Universität, Jena, Germany.)

Of 369 patients with cancer of the breast irradiated between 1950 and 1955, 4 developed spontaneous fractures of the ribs and clavicle attributed to radionecrosis. The author agrees with previous reports that doses of 1,800–4,000 r can produce such spontaneous fractures and that they may appear as early as twelve months after irradiation. Clinically, these fractures tend to be silent and to be discovered on follow-up chest roentgenograms.—*Henry G. Moehring, M.D.*

RADIOISOTOPES

Walfish, Paul G., Britton, Amy, Volpe, Robert, and Ezrin, Calvin. Experience with an *in vitro* test of thyroid function—the red blood cell uptake of L-triiodothyronine labelled with radioactive iodine. *Canad. M. A. J.*, Mar. 25, 1961, *84*, 637–641. (From: Departments of Medicine and Pathological Chemistry of the University of Toronto and the Clinical Investigation Units of Sunnybrook (D.V.A.) and Toronto General Hospitals, Toronto, Ontario, Canada.)

While the technical procedures of this test are directed at determining the radioactivity of washed erythrocytes following incubation with T_3-I^{131} and calculating the percentage uptake, it is felt that the test really measures indirectly the ability of certain unsaturated plasma proteins to bind added T_3-I^{131}.

In this study, 240 determinations of the R.C.U. (red cell uptake) of T_3-I^{131}, performed according to the method of Hamolsky *et al.*, revealed that 89 per cent in the euthyroid group were within the range of 12.5–18.5 per cent uptake. Eighty-three per cent of the hyperthyroid group had greater than 18.5 per cent uptake with all the normal R.C.U. values occurring in the untreated nodular and previously treated diffuse thyrotoxic patients. In the hypothyroid group, 77 per cent had less than 12.5 per cent uptake; three quarters of those with normal R.C.U. values had recently received thyroid hormone therapy. For the most accurate and reproducible results, the authors recommend that the test be performed on the blood within twenty-four hours of sampling and that silicone glassware be used throughout.

The chief advantages of the R.C.U. test over other tests of thyroid function are: (1) it is not significantly influenced by iodine contamination; (2) it avoids the administration of a radioactive material to the patient; (3) it measures another aspect of thyroid physiology.

Clinical factors which reportedly have no significant effect on the R.C.U. result are colloid and nontoxic nodular goiters, thyroid carcinoma, exogenous iodine, anxiety, congestive heart failure (without hepatic failure), hypertension, administrations of mercury, and some endocrinopathies.

A significant decrease in the R.C.U. has been demonstrated during normal pregnancy, functional hyperestrogen states, and propylthiouracil or iodine therapy for hyperthyroidism.

A significant increase in the R.C.U. may occur if the patient is taking anticoagulants, or is suffering from renal disease (especially nephrosis), severe liver disease, severe metastatic malignancy, severe pulmonary insufficiency, paroxysmal atrial arrhythmias, or polycythemia rubra vera.

An addendum to the article reviews a newly published method of calculating an improved hematocrit correction for use in this test. This new method is most valuable when the hematocrit is outside the 30–40 per cent range.—*Donald M. Monson, M.D.*

Rosenthall, Leonard. A rapid screening method for I^{131} fat-absorption test. *Radiology*, Feb., 1961, *76*, 251–254. (Address: Ontario Cancer Institute, Princess Margaret Hospital, 500 Sherbourne Street, Toronto 5, Ontario, Canada.)

The usual method for determining small bowel absorbability of an oral test dose of I^{131} tagged triolein is to take blood samples at three, four, five, and six hours after ingestion. The total blood activity is then compared with normal values. The author states that, with oral doses of about 20 μc, enough activity was present at the end of three hours to be counted by means of a scintillation detector probe placed against the head. A linear relationship was found to exist between the number of microcuries in the blood and the head counts. The examination is terminated in patients having normal head counts at the end of three hours, while venipuncture is done as usual with those patients whose head counts indicate a low activity.

The author presents details of his study in determining normal head counts in 32 patients. After three hours the relationship is not accurate, as iodine is deposited in the brain. The exact relationships must be determined by the individual laboratory.—*James C. Moore, M.D.*

Wagner, Henry N., Jr., McAfee, John G., and Mozley, James M. Diagnosis of liver disease by radioisotope scanning. *A.M.A. Arch. Int. Med.*, Mar., 1961, *107*, 324–334. (From: Diagnostic Radioisotope Laboratory, Johns Hopkins Hospital, Baltimore, Md.)

The authors use an automatic photoscanning device (which records on x-ray film) to detect and evaluate suspected diseases in the upper quadrant of the abdomen. The patient is given 100 μc of either rose bengal or colloidal radioactive gold intravenously. The scan film is superimposed on an anteroposterior supine roentgenogram of the patient's abdomen and lower chest. The authors demonstrate in 19 different figures how these composite pictures can aid in the diagnosis of upper abdominal disease.

This article also illustrates how the demonstration of filling defects in the liver has aided in the diagnosis of pyelogenic abscess of the liver, amebiasis, primary and metastatic tumor from the liver, and vascular anomalies. The position of the liver has helped in the detection of a subphrenic abscess and congenital malposition of the liver, and it has served to differentiate lower lobe pneumonias from sub-

phrenic abscesses. The authors demonstrate how they use this technique for the differential diagnosis of abdominal masses, for differentiation between obstruction and parenchymal liver disease, and for preoperative evaluation of patients with suspected liver malignancies. In addition, they illustrate the use of this technique in demonstrating Riedel's lobe of the liver, in localizing therapy ports, in evaluating the effect of chemotherapy on liver metastasis and in differentiating between mild and severe infectious hepatitis.

If the necessary equipment is available the technique is fast and simple; it is easy for the operator to perform and for the patient to undergo. The radiation dose is less than that from routine roentgen studies, except in the case of a patient with complete biliary obstruction. Therefore, this procedure is another practical and effective aid to the physician trying to make a definitive diagnosis in suspected disease of the uper abdomen.—*William W. Joule, M.D.*

Frost, Dietrich, and Werkes, Heinz. Über ein neues Verfahren zur Darstellung schwach speichernder Gewebe in der Gamma-Szintigraphie. (A new arrangement for gamma-scintigraphic delineation of tissues with relatively low uptake.) *Strahlentherapie*, Nov., 1960, *113*, 461–468. (From: Abteilung für Strahlungsphysik des Städt. Rudolf-Virchow-Krankenhauses Berlin and Entwicklungsabteilung der Dr. H. Stamm K. G., Berlin, Germany.)

Scintigraphic and photogammagraphic distinction between normal and abnormal tissues, when the differential uptake of radioactive material is slight, depends on suppressing background signals (which arise from the surrounding "normal" tissues) and then improving contrast between the useful signals by steepening the differential curve between impulse rates from the "abnormal" tissue and from its edges.—*Henry G. Moehring, M.D.*

Bogasch, U., Käsbauer, H., and Künlen, H. Erfahrungen mit der Radiogoldspickung der Hypophyse bei metastasierenden Neoplasmen unter besonderer Berücksichtigung des Mammakarzinoms. (Experiences with radiogold seeding of the hypophysis in metastasizing neoplasms with special consideration of mammary carcinoma.) *München. med. Wchnschr.*, Jan., 1961, *103*, 147–150. (From: Chirurgische Abteilung des Städt. Krankenhauses München r. d. Isar and Strahlenabteilung des Städt. Krankenhauses München r. d. Isar, Germany.)

Sex hormones influence the growth and function of glandular carcinoma, especially of the breast. The aim of therapy, therefore, is to eliminate the follicular hormone. Administration of male hormones only impairs but does not suppress the formation of estrogen. Ovariectomy is of temporary benefit because the hyperplastic adrenal cortex soon starts producing steroids.

Suppression of the pituitary hormone remains as the most effective approach since this causes atrophy of the adrenal cortex and of the ovary. Removal of the hypophysis is compatible with life, although prolactine and the growth hormone are eliminated.

Surgical extirpation of the gland is associated with a high mortality. Electrocoagulation is not reliable and roentgen therapy is inadequate. Therefore, the application of radioactive isotopes has become the method of choice. The authors prefer radiogold to the yttrium isotope and injection via a percutaneous rather than a transnasal route. To prevent damage to the optic nerves and other vital structures, the dosage is kept to a minimum of three seeds of Au^{198} (10 mc each).

Forty-eight patients were treated in the past four years: 35 cancers of the breast, 10 of the ovary, 2 of the cervix and 1 of the colon. The results were disappointing in tumors of the ovary, uterus, and colon.

Criteria for remission were general improvement and regression of metastases for at least one year. There were only 2 definite remissions with the disappearance of metastatic nodes and filling in of osteolytic foci. The 2 cases are illustrated by serial roentgenograms taken over a period of several years. Two-thirds of the patients improved subjectively and one-third was not influenced.

Spontaneous remissions may occasionally occur in similar far advanced cases, but the results in the cited 2 patients were so impressive that the authors extended the indication for hypophyseal sterilization to less advanced cases. Thus, they hope that their final statistical results will compare favorably with those of other investigators.

There was no primary mortality due to the treatment. Transient postoperative headache, which was frequently observed, responded to sodium chloride infusions and vitamin medication. As to side effects, there were single cases of diabetes insipidus, retrobulbar hematoma, paresis of an oculomotor nerve, and 3 cases with transient fistulae of cerebrospinal fluid.

A special advantage of radiogold seeding is the fact that the operation can be repeated if necessary. There is no age limit, as proved by 2 patients who were seventy-five years old. The method, however, is contraindicated in terminal cases with metastatic involvement of the liver, lungs, and brain.—*Ernest Kraft, M.D.*

Miscellaneous

Stewart, Alice. Aetiology of childhood malignancies; congenitally determined leukaemias. *Brit. M. J.*, Feb. 18, 1961, *1*, 452–460. (Address: Dr. Alice Stewart, Reader in Social Medicine, Oxford University, Oxford, England.)

The survey data which first suggested that prenatal roentgen-ray exposure increased the risk of childhood malignancies also showed that leukemia is exceptionally common among mongoloids (Stewart, Webb, Hewitt, 1958) with the implication that for some cases of leukemia the decisive event dated back to the onset of mongolism.

The Rous theory of cocarcinogenesis assumes two stages in the development of cancers (Rous and Kidd, 1941)—"initiation" and "promotion." If this idea were applied to the concept of gene mutations, the sequence of events might be as follows. "Initiators" cause a mutation within a germinal cell but this remains silent until fertilization, when one of four things should occur: (1) miscarriage; (2) cancer development *in utero* or after birth; (3) development of premalignant disease (*e.g.*, intestinal polyposis); or (4) a normal phenotype with an abnormal genotype.

These ideas have been incorporated in the working hypothesis for childhood malignancies:

(1) Malignant diseases are "initiated" by roentgen rays and other mutagens before conception (prezygotic), during pregnancy (postzygotic) or after birth.
(2) In childhood, the chief promoter is the cell stress of embryogenesis; therefore, most cancers and leukemias are prezygotic.
(3) At all ages, infection stresses the leukocyte and promotes leukemia. Mongoloids have increased susceptibility to infection so mongolism indirectly promotes leukemia. Because mongolism is inherited, it is more likely to affect prezygotic than postzygotic leukemias.
(4) Prezygotic carcinomas and leukemias favor primitive cell types and may have familial incidence. Postzygotic carcinomas and leukemias favor mature cell types and have no familial incidence.
(5) No normal leukocytes are present in individuals with prezygotic leukemias, so there is exceptionally low resistance to infection.
(6) Recent increases in childhood leukemias reflect a falling death rate for pneumonias and infection and are due to prezygotic leukemias.

Two types of childhood leukemia are identified: (1) The more common variety of leukemia with lymphoblasts or monoblasts is derived from stem and blast cells. These cases (most frequently boys—frequently familial—often mongoloids) are prone to infection. It is postulated that prezygotic leukemias are due to a gene inheritance which produces premalignant changes in ancestral cells of the reticuloendothelial system. During embryogenesis further changes occur in these abnormal cells leading to malignancy. If the abnormal cell survives embryogenesis, it may become malignant under subsequent leukocyte stress, such as infection, or remain indefinitely in a premalignant stage. (2) In postzygotic leukemias, the cells may be myeloblasts, lymphoblasts or stem cells. These cases are not associated with mongolism, have no familial incidence, and are less susceptible to infection than those in the first category. It is postulated that these leukemias are due to changes in premalignant somatic cells. The unaffected leukocytes in these children behave normally during infection.

The final conclusion is that the role of leukocytes in pyogenic infections and the profound changes following the use of antibiotics have led to a discovery of a leukemia variety in which the first event predates conception and produces a preleukemic gene. The prezygotic leukemias derived from these genes are responsible for the early peak of leukemia mortality (two to four years) and have their counterpart in other cancers. It is also suggested that in any population the numbers of preleukemic genes and the number of prezygotic leukemias are to a large extent controlled by the prevalence of and mortality from pyogenic infections.—*Bernard Loitman, M.D.*